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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07K 14/705, C12N 15/12, C12Q 1/68, C12N 5/10, C07K 16/28, G01N 33/53, A61K 38/17

A2

(11) International Publication Number: **WO 00/40614**

(43) International Publication Date: 13 July 2000 (13.07.00)

(21) International Application Number: PCT/US99/29996

(22) International Filing Date: 20 December 1999 (20.12.99)

(30) Priority Data:

60/114,220	30 December 1998 (30.12.98)	US
60/120,018	29 January 1999 (29.01.99)	US
60/140,415	22 June 1999 (22.06.99)	US

(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
Without international search report and to be republished upon receipt of that report.

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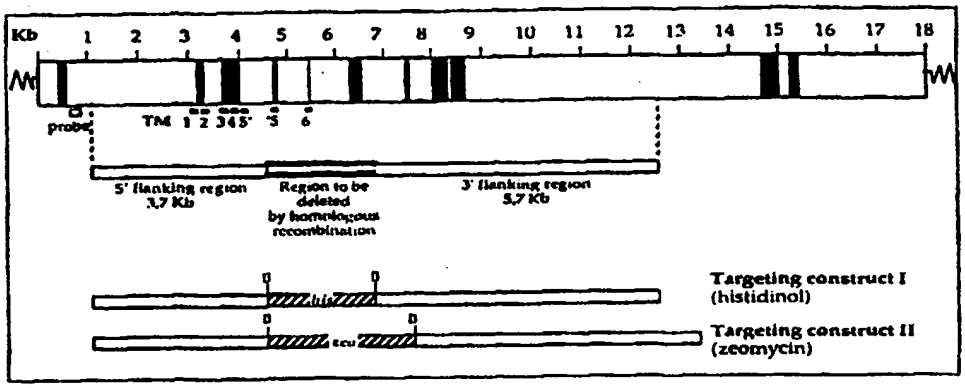
(54) Title: CHARACTERIZATION OF A CALCIUM CHANNEL FAMILY



(57) Abstract

Nucleic acids encoding SOC/CRAC calcium channel polypeptides, including fragments and biologically functional variants thereof and encoded polypeptides are provided. The nucleic acids and polypeptides disclosed herein are useful as therapeutic and diagnostic agents. Agents that selectively bind to the foregoing polypeptides and genes also are provided.

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CHARACTERIZATION OF A CALCIUM CHANNEL FAMILY

Field of the Invention

This invention relates to nucleic acids coding for a novel family of calcium channel polypeptides, the encoded polypeptides, unique fragments of the foregoing, and methods of making and using same.

Background of the Invention

Calcium channels are membrane-spanning, multi-subunit proteins that facilitate the controlled transport ("flux") of Ca^{2+} ions into and out of cells. Cells throughout the animal kingdom, and at least some bacterial, fungal and plant cells, possess one or more types of calcium channels. In general, "excitable" cells, such as neurons of the central nervous system, peripheral nerve cells, and muscle cells, including those of skeletal muscles, cardiac muscles, and venous and arterial smooth muscles, possess voltage-dependent calcium channels. In a voltage-dependent calcium channel, the transport of Ca^{2+} ions into and out of the cells requires a certain minimal level of depolarization (the difference in potential between the inside of the cell bearing the channel and the extracellular environment) with the rate of Ca^{2+} cell flux dependent on the difference in potential. In "non-excitable" cells, calcium influx is thought to occur predominantly in response to stimuli which cause the release of calcium from intracellular stores. This process, termed *store operated calcium influx,* is not well understood.

Characterization of a particular type of calcium channel by analysis of whole cells is complicated by the presence of mixed populations of different types of calcium channels in the majority of cells. Although single-channel recording methods can be used to examine individual calcium channels, such analysis does not reveal information related to the molecular structure or biochemical composition of the channel. Furthermore, in this type of analysis, the channel is isolated from other cellular constituents that might be important for the channel's natural functions and pharmacological interactions. To study the calcium channel structure-function relationship, large amounts of pure channel protein are needed. However, acquiring large amounts of pure protein is difficult in view of the complex nature of these multisubunit proteins, the varying concentrations of calcium channel proteins in tissue sources, the presence of mixed populations of calcium channel proteins in tissues, and the modifications of the native protein that can occur during the isolation procedure.

Summary of the Invention

The invention is based on the identification of a novel family of calcium channel polypeptides and the molecular cloning and partial characterization of a novel member of this family that is expressed predominantly in human hematopoietic cells, liver, and kidney. This newly identified family of calcium channel polypeptides is designated, "SOC" or "CRAC" or "ICRAC", for Store Operated Channels or Calcium Release Activated Channels. Although not wishing to be bound to any particular theory or mechanism, it is believed that the SOC/CRAC calcium channel polypeptides are transmembrane polypeptides that modulate Ca^{2+} flux "into" and "out of" a cell, for example, in certain instances they may be activated upon depletion of Ca^{2+} from intracellular calcium stores, allowing Ca^{2+} influx into the cell. Accordingly, the compositions disclosed herein are believed to be useful for modulating calcium transport into and out of such intracellular stores and for the treatment of disorders that are characterized by aberrant calcium transport into and out of such intracellular stores. In particular, we believe that the SOC/CRAC calcium channel polypeptides disclosed herein play an important role in the influx of extracellular calcium by mediating the refilling of intracellular calcium stores following their depletion. Accordingly, we believe that the compositions for expressing functional SOC/CRAC calcium channel polypeptides in cells, as disclosed herein, are useful for treating patients having conditions that are characterized by reduced extracellular calcium influx into their SOC/CRAC-expressing cells. Additionally, the compositions of the invention are useful for delivering therapeutic and/or imaging agents to cells which preferentially express SOC/CRAC calcium channel polypeptides and, in particular, for delivering such agents to hematopoietic cells, liver, heart, spleen, and kidney to modulate proliferation and growth of these cells. Moreover, in view of the importance of cellular calcium levels to cell viability, we believe that SOC-2/CRAC-1, SOC-3/CRAC-2, and SOC-4/CRAC-3 as disclosed herein, and/or other members of the SOC/CRAC family of calcium channel polypeptides, represent an ideal target for designing and/or identifying (e.g., from molecular libraries) small molecule inhibitors that block lymphocyte proliferation, as well as other binding agents that selectively bind to SOC/CRAC polypeptides to which drugs or toxins can be conjugated for delivery to SOC/CRAC polypeptide expressing cells.

The invention is based, in part, on the molecular cloning and sequence analysis of the novel SOC/CRAC calcium channel molecules disclosed herein (also referred to as a "SOC-2/CRAC-1 molecule," a "SOC-3/CRAC-2 molecule," and/or "SOC-4/CRAC-3 molecule") that are predominantly expressed in human hematopoietic cells, liver, spleen, heart, and

kidney (SOC-2/CRAC-1), kidney and colon (SOC-3/CRAC-2), and prostate (SOC-4/CRAC-3 molecule). As used herein, a "SOC/CRAC molecule" embraces a "SOC/CRAC calcium channel nucleic acid" (or "SOC/CRAC nucleic acid") and a "SOC/CRAC calcium channel polypeptide" (or "SOC/CRAC polypeptide"). Homologs and alleles also are embraced within the meaning of a SOC/CRAC calcium channel molecule.

According to one aspect of the invention, isolated SOC/CRAC nucleic acids which code for one or more member(s) of the SOC/CRAC family of calcium channel polypeptides or unique fragments thereof are provided. The isolated nucleic acids refer to one or more of the following:

(a) nucleic acid molecules which hybridize under stringent conditions to a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, and which code for a SOC/CRAC polypeptide;

(b) deletions, additions and substitutions of (a) which code for a respective SOC/CRAC polypeptide;

(c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) in codon sequence due to the degeneracy of the genetic code, and

(d) complements of (a), (b) or (c).

The invention in another aspect provides an isolated nucleic acid molecule selected from the group consisting of (a) a unique fragment of a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:29, and SEQ ID NO:31, (b) complements of (a), provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to any sequence selected from a sequence group consisting of (1) sequences having the SEQ. ID NOS. or GenBank accession numbers of Table I, (2) complements of (1), and (3) fragments of (1) and (2).

According to yet another aspect of the invention, isolated SOC/CRAC polypeptides are provided. The isolated SOC/CRAC polypeptide molecules are encoded by one or more SOC/CRAC nucleic acid molecules of the invention. Preferably, the SOC/CRAC polypeptide contains one or more polypeptides selected from the group consisting of the polypeptides having SEQ. ID Nos. 2, 4, 6, 8, 24, 26, 28, 30, and 32. In other embodiments, the isolated polypeptide may be a fragment or variant of the foregoing SOC/CRAC polypeptide molecules of sufficient length to represent a sequence unique within the human genome, and identifying

with a polypeptide that functions as a calcium channel, provided that the fragment excludes a sequence of contiguous amino acids identified in Table II, and/or excludes a sequence of contiguous amino acids encoded for by a nucleic acid sequence identified in Table I. In another embodiment, immunogenic fragments of the polypeptide molecules described above are provided.

According to another aspect of the invention, isolated SOC/CRAC binding agents (e.g., polypeptides) are provided which selectively bind to a SOC/CRAC molecule (e.g., a SOC/CRAC polypeptide encoded by the isolated nucleic acid molecules of the invention). Preferably, the isolated binding agents selectively bind to a polypeptide which comprises the sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32, or unique fragments thereof. In the preferred embodiments, the isolated binding polypeptides include antibodies and fragments of antibodies (e.g., Fab, $F(ab)_2$, Fd and antibody fragments which include a CDR3 region which binds selectively to a SOC/CRAC polypeptide). Preferably, the antibodies for human therapeutic applications are human antibodies.

According to another aspect of the invention, a pharmaceutical composition containing a pharmaceutically effective amount of an isolated SOC/CRAC nucleic acid, an isolated SOC/CRAC polypeptide, or an isolated SOC/CRAC binding polypeptide in a pharmaceutically acceptable carrier also is provided. The pharmaceutical compositions are useful in accordance with therapeutic methods disclosed herein.

According to yet another aspect of the invention, a method for isolating a SOC/CRAC molecule is provided. The method involves:

a) contacting a SOC/CRAC nucleic acid or a SOC/CRAC binding polypeptide with a sample that is believed to contain one or more SOC/CRAC molecules, under conditions to form a complex of the SOC/CRAC nucleic acid or the SOC/CRAC binding polypeptide and the SOC/CRAC molecule;

b) detecting the presence of the complex;

c) isolating the SOC/CRAC molecule from the complex; and

d) determining whether the isolated SOC/CRAC molecule has SOC/CRAC calcium channel activity. As used herein "SOC/CRAC calcium channel activity" refers to the transport of Ca^{2+} into and out of intracellular stores that is mediated by a SOC/CRAC

polypeptide. In general, the SOC/CRAC calcium channel activity is initiated by a reduction or depletion of intracellular calcium stores.

In certain embodiments, the SOC/CRAC nucleic acid is a SOC-2/CRAC-1 nucleic acid (e.g., a nucleic acid having SEQ. ID NO. 27, or complements thereof); in certain other embodiments, the SOC/CRAC nucleic acid is a SOC-3/CRAC-2 nucleic acid (e.g., a nucleic acid having SEQ. ID NO. 29, or complements thereof); in further embodiments, the SOC/CRAC nucleic acid is a SOC-4/CRAC-3 nucleic acid (e.g., a nucleic acid having SEQ. ID NO. 31, or complements thereof). In yet other embodiments, the SOC/CRAC polypeptide is a SOC-2/CRAC-1 binding polypeptide (e.g., an antibody that selectively binds to a SOC-2/CRAC-1 polypeptide). In yet further embodiments, the SOC/CRAC polypeptide is a SOC-3/CRAC-2 binding polypeptide (e.g., an antibody that selectively binds to a SOC-3/CRAC-2 polypeptide). In some embodiments, the SOC/CRAC polypeptide is a SOC-4/CRAC-3 binding polypeptide (e.g., an antibody that selectively binds to a SOC-4/CRAC-3 polypeptide). In the preferred embodiments, the isolated binding polypeptides include antibodies and fragments of antibodies (e.g., Fab, $F(ab)_2$, Fd and antibody fragments which include a CDR3 region which binds selectively to a SOC-2/CRAC-1, to a SOC-3/CRAC-2, and/or to a SOC-4/CRAC-3 polypeptide). Preferably the isolated binding polypeptides or other binding agents selectively bind to a single SOC/CRAC molecule, i.e., are capable of distinguishing between different members of the SOC/CRAC family. Accordingly, one or more SOC/CRAC binding agents can be contained in a single composition (e.g., a pharmaceutical composition) to identify multiple SOC/CRAC molecules *in vivo* or *in vitro*.

According to yet another aspect of the invention, a method for identifying agents useful in the modulation of SOC/CRAC calcium channel activity is provided. The method involves:

a) contacting a SOC/CRAC polypeptide with a candidate agent suspected of modulating SOC/CRAC calcium channel activity, under conditions sufficient to allow the candidate agent to interact selectively with (e.g. bind to) the SOC/CRAC polypeptide;

b) detecting a Ca^{2+} concentration of step (b) associated with the SOC/CRAC calcium channel activity of the SOC/CRAC polypeptide in the presence of the candidate agent; and

c) comparing the Ca^{2+} concentration of step (b) with a control Ca^{2+} concentration of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the candidate agent modulates (increases or decreases) SOC/CRAC calcium channel activity.

According to another aspect of the invention, a method for identifying agents useful in the modulation of a SOC/CRAC polypeptide kinase activity is provided. The method involves:

a) contacting a SOC/CRAC polypeptide with kinase activity with a candidate agent suspected of modulating SOC/CRAC kinase activity, under conditions sufficient to allow the candidate agent to interact with the SOC/CRAC polypeptide and modulate its kinase activity;

b) detecting a kinase activity associated with the SOC/CRAC polypeptide in the presence of the candidate agent; and

c) comparing the kinase activity of step (b) with a control kinase activity of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the candidate agent modulates (increases or decreases) SOC/CRAC kinase activity. In some embodiments the SOC/CRAC polypeptide comprises amino acids 999-1180 of the SOC-2/CRAC-1 polypeptide (SEQ ID NO:24), or a fragment thereof that retains the kinase activity.

According to yet another aspect of the invention, a method for determining the level of expression of a SOC/CRAC polypeptide in a subject is provided. The method involves:

a) measuring the expression of a SOC/CRAC polypeptide in a test sample, and

b) comparing the measured expression of the SOC/CRAC polypeptide in the test sample to the expression of a SOC/CRAC polypeptide in a control containing a known level of expression to determine the level of SOC/CRAC expression in the subject. Expression is defined as SOC/CRAC mRNA expression or SOC/CRAC polypeptide expression. Various methods can be used to measure expression. The preferred embodiments of the invention utilize PCR and Northern blotting for measuring mRNA expression, and monoclonal or polyclonal SOC/CRAC antisera as reagents for measuring SOC/CRAC polypeptide expression. In preferred embodiments, the SOC/CRAC molecule (nucleic acid and/or polypeptide) is SOC-2/CRAC-1. In other preferred embodiments, the SOC/CRAC molecule is SOC-3/CRAC-2. In yet further preferred embodiments, the SOC/CRAC molecule is SOC-4/CRAC-3. In certain embodiments, the test samples include biopsy samples and biological fluids such as blood. The method is useful, e.g., for assessing the presence or absence or stage of a proliferative disorder in a subject.

The invention also contemplates kits comprising a package including assays for SOC/CRAC epitopes, SOC/CRAC nucleic acids, and instructions, and optionally related materials such as controls, for example, a number, color chart, or an epitope of the expression product of the foregoing isolated nucleic acid molecules of the invention for comparing, for

example, the level of SOC/CRAC polypeptides or SOC/CRAC nucleic acid forms (wild-type or mutant) in a test sample to the level in a control sample having a known amount of a SOC/CRAC nucleic acid or SOC/CRAC polypeptide. This comparison can be used to assess in a subject a risk of developing a cancer or the progression of a cancer. The kits may also include assays for other known genes, and expression products thereof, associated with, for example, proliferative disorders (e.g., BRCA, p53, etc.). In a preferred embodiment, the kit comprises a package containing: (a) a binding agent that selectively binds to an isolated nucleic acid of the invention or an expression product thereof to obtain a measured test value, (b) a control containing a known amount of a SOC/CRAC nucleic acid or a SOC/CRAC polypeptide to obtain a measured control value, and (c) instructions for comparing the measured test value to the measured control value to determine the amount of SOC/CRAC nucleic acid or expression product thereof in a sample.

The invention provides isolated nucleic acid molecules, unique fragments thereof, expression vectors containing the foregoing, and host cells containing the foregoing. The invention also provides isolated binding polypeptides and binding agents which bind such polypeptides, including antibodies, and pharmaceutical compositions containing any of the compositions of the invention. The foregoing can be used, *inter alia,* in the diagnosis or treatment of conditions characterized by the aberrant expression levels and/or the presence of mutant forms of a SOC/CRAC nucleic acid or polypeptide. The invention also provides methods for identifying agents that alter the function of the SOC/CRAC polypeptide.

These and other aspects of the invention, as well as various advantages and utilities, will be more apparent with reference to the detailed description of the preferred embodiments.

Brief Description of the Sequences

SEQ ID NO:1 is a partial nucleotide sequence of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:2 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:1).

SEQ ID NO:3 is a partial nucleotide sequence of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:4 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:3).

SEQ ID NO:5 is a partial nucleotide sequence of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:6 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:5).

SEQ ID NO:7 is a partial nucleotide sequence of the mouse homologue (mSOC-2/CRAC-1) of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:8 is the predicted amino acid sequence of the translation product of the mSOC-2/CRAC-1 cDNA (SEQ ID NO:7).

SEQ ID NO:9 is the nucleotide sequence of the mouse MLSN-1 (SOC-1) cDNA.

SEQ ID NO:10 is the predicted amino acid sequence of the translation product of the mouse MLSN-1 (SOC-1) cDNA (SEQ ID NO:9).

SEQ ID NO:11 is the nucleotide sequence of a human calcium channel cDNA with GenBank Acc. no.: AB001535.

SEQ ID NO:12 is the predicted amino acid sequence of the translation product of the human calcium channel cDNA with GenBank Acc. no.: AB001535 (SEQ ID NO:11).

SEQ ID NO:13 is the amino acid sequence of a *C. Elegans* polypeptide at the c05c12.3 locus.

SEQ ID NO:14 is the amino acid sequence of a *C. Elegans* polypeptide at the F54D1 locus.

SEQ ID NO:15 is the amino acid sequence of a *C. Elegans* polypeptide at the t01H8 locus.

SEQ ID NO:16 is the nucleotide sequence of a mouse kidney cDNA with GenBank Acc. no.: AI226731.

SEQ ID NO:17 is the predicted amino acid sequence of the translation product of the mouse kidney cDNA with GenBank Acc. no.: AI226731 (SEQ ID NO:16).

SEQ ID NO:18 is the nucleotide sequence of a human brain cDNA with GenBank Acc. no.: H18835.

SEQ ID NO:19 is the predicted amino acid sequence of the translation product of the human brain cDNA with GenBank Acc. no.: H18835 (SEQ ID NO:18).

SEQ ID NO:20 is the nucleotide sequence of the human EST with GenBank Acc. no.: AA419592.

SEQ ID NO:21 is the nucleotide sequence of the human EST with GenBank Acc. no.: AA419407.

SEQ ID NO:22 is the nucleotide sequence of the mouse EST with GenBank Acc. no.: AI098310.

SEQ ID NO:23 is a partial nucleotide sequence of the human SOC-2/CRAC-1 cDNA that contains the SOC-2/CRAC-1 sequences of SEQ ID NO:1, SEQ ID NO:3, and SEQ ID NO:5.

SEQ ID NO:24 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:23).

SEQ ID NO:25 is a partial nucleotide sequence of the human SOC-3/CRAC-2 cDNA.

SEQ ID NO:26 is the predicted amino acid sequence of the translation product of human SOC-3/CRAC-2 cDNA (SEQ ID NO:25).

SEQ ID NO:27 is the full nucleotide sequence of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:28 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:27).

SEQ ID NO:29 is the full nucleotide sequence of the human SOC-3/CRAC-2 cDNA.

SEQ ID NO:30 is the predicted amino acid sequence of the translation product of human SOC-3/CRAC-2 cDNA (SEQ ID NO:29).

SEQ ID NO:31 is the full nucleotide sequence of the human SOC-4/CRAC-3 cDNA.

SEQ ID NO:32 is the predicted amino acid sequence of the translation product of human SOC-4/CRAC-3 cDNA (SEQ ID NO:31).

Brief Description of the Drawings

Figure 1 is a schematic depicting the intron/exon organization of the chicken SOC-2/CRAC-1 genomic sequence, as well as the putative transmembrane (TM) domains, and the targeting constructs utilized in the knockout experiments.

Detailed Description of the Invention

One aspect of the invention involves the partial cloning of cDNAs encoding members of a novel family of calcium channel polypeptides, referred to herein as "SOC/CRAC" (designated "SOC" or "CRAC" or "ICRAC", for Store Operated Channels or Calcium Release Activated Channels, or CECH). Although not intending to be bound to any particular mechanism or theory, we believe that a SOC/CRAC family member is a transmembrane calcium channel that modulates Ca^{2+} flux "into" and "out of" a cell; in certain instances it may be activated upon depletion of Ca^{2+} from intracellular calcium stores, allowing Ca^{2+} influx into the cell.

The first three isolated SOC/CRAC members disclosed herein, define a new family of calcium channels which is distinct from previously described calcium channels, such as voltage gated calcium channels, ryanodine receptor/inositol-1,4,5-triphosphate receptor

channels, and Transient Receptor Potential (TRP) channels. The SOC/CRAC family of calcium channels exhibits high selectivity (with a P_{Ca}/P_{Na} ratio near 1000), a unitary conductance below the detection level of the patch clamp method (the conductance estimated at approximately 0.2 picosiemens), and are subject to inhibition by high intracellular calcium levels. Although not intending to be bound to any particular mechanism or theory, we believe that SOC/CRAC calcium channels are responsible for the majority of, for example, calcium entry which occurs when intracellular calcium stores are depleted, and that SOC/CRAC currents are important for initiating various types of calcium-dependent processes. Thus, we believe that SOC/CRAC calcium channels play an important role in cellular calcium homeostasis by, e.g., modulating the supply of calcium to refill intracellular stores when depleted.

The isolated full-length sequence of a representative, first member of the SOC/CRAC family, human SOC/CRAC nucleic acid (cDNA), SOC-2/CRAC-1, is represented as the nucleic acid of SEQ ID NO:27. This nucleic acid sequence codes for the SOC-2/CRAC-1 polypeptide with the predicted amino acid sequence disclosed herein as SEQ ID NO:28. A homologous mouse cDNA sequence (>90% identity to the human at the nucleotide level) is represented as the nucleic acid of SEQ ID NO:7, and codes for a unique fragment of a mouse SOC-2/CRAC-1 polypeptide having the predicted, partial amino acid sequence represented as SEQ ID NO:8. Analysis of the SOC-2/CRAC-1 partial sequence by comparison to nucleic acid and protein databases show that SOC-2/CRAC-1 shares a limited homology to mouse MLSN-1 (SOC-1, SEQ ID NOs: 9 and 10). Limited homology is also shared between SOC-2/CRAC-1 and three *C. Elegans* polypeptides (SEQ ID NOs: 13, 14, and 15). We further believe that SOC-2/CRAC-1 plays a role in the regulation of cellular Ca^{2+} fluxing and, in particular, lymphocyte Ca^{2+} fluxing.

A second member of the human SOC/CRAC family of calcium channels, SOC-3/CRAC-2, is represented as the nucleic acid of SEQ ID NO:29, and codes for the human SOC-3/CRAC-2 polypeptide having the predicted amino acid sequence represented as SEQ ID NO:30 (this molecule may also be referred to as CECH2). SOC-3/CRAC-2 is predominantly expressed in human hematopoietic cells (including peripheral blood lymphocytes, liver, bone marrow, spleen, thymus, lymph nodes, heart, and kidney. Expression can also be detected (at lesser levels) in brain, skeletal muscle colon, small intestine, placenta, lung, and cells (cell lines) such as HL-60, HeLa, K562, MOLT-4, SW-480, A459, and G361.

A third member of the human SOC/CRAC family of calcium channels, SOC-4/CRAC-3, is represented as the nucleic acid of SEQ ID NO:31, and codes for the human SOC-4/CRAC-3 polypeptide having the predicted amino acid sequence represented as SEQ ID NO:32 (this molecule may also be referred to as CECH6). It specifically expressed in the prostate gland/cells.

As used herein, a SOC/CRAC calcium channel nucleic acid (also referred to herein as a "SOC/CRAC nucleic acid" refers to a nucleic acid molecule which: (1) hybridizes under stringent conditions to one or more of the nucleic acids having the sequences of SEQ. ID NOS. 7, 27, 29, and/or 31 (sequences of the mouse and human SOC-2/CRAC-1, human SOC-3/CRAC-2, and human SOC-4/CRAC-3 nucleic acids), and (2) codes for a SOC-2/CRAC-1, a SOC-3/CRAC-2 or a SOC-4/CRAC-3 calcium channel polypeptide, respectively, or unique fragments of said SOC-2/CRAC-1, SOC-3/CRAC-2, or SOC-4/CRAC-3 polypeptide.

As used herein, a SOC/CRAC calcium channel polypeptide (also referred to herein as a "SOC/CRAC polypeptide") refers to a polypeptide that is coded for by a SOC-2/CRAC-1 , a SOC-3/CRAC-2, and/or a SOC-4/CRAC-3 nucleic acid. Preferably, the above-identified SOC/CRAC polypeptides mediate transport of calcium into and out of a cell.

SOC/CRAC polypeptides also are useful as immunogenic molecules for the generation of binding polypeptides (e.g., antibodies) which bind selectively to SOC/CRAC (e.g., SOC-2/CRAC-1, SOC-3/CRAC-2, and/or SOC-4/CRAC-3) polypeptides. Such antibodies can be used in diagnostic assays to identify and/or quantify the presence of a SOC/CRAC polypeptide in a sample, such as a biological fluid or biopsy sample. SOC/CRAC polypeptides further embrace functionally equivalent fragments, variants, and analogs of the preferred SOC/CRAC polypeptides, provided that the fragments, variants, and analogs also are useful in mediating calcium transport into and out of intracellular calcium stores.

As used herein, "SOC/CRAC calcium channel activity" refers to Ca^{2+} transport ("Ca^{2+} fluxing") across the plasma membrane that is mediated by a SOC/CRAC calcium channel polypeptide. The SOC/CRAC calcium channel polypeptide typically has one or more of the following properties: high selectivity, a unitary conductance below the detection level of the patch clamp method,and are subject to inhibition by high intracellular calcium levels. Such activity can be easily detected using standard methodology well known in the art. See, e.g., the Examples and Neher, E., "Ion channels for communication between and within cells",

Science, 1992; 256:498-502; and Hoth, M., and Penner, R., "Depletion of intracellular calcium stores activates a calcium current in mast cells", Nature, 1992; 355 (6358):353-6.

According to one aspect of the invention, isolated nucleic acid molecules which code for one or more member(s) of the SOC/CRAC family of calcium channel polypeptides are provided. The isolated nucleic acid molecules are selected from the following groups:

(a) nucleic acid molecules which hybridize under stringent conditions to one or more nucleic acid molecules selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, and which code for a SOC/CRAC polypeptide;

(b) deletions, additions and substitutions of (a) which code for a respective SOC/CRAC polypeptide;

(c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) in codon sequence due to the degeneracy of the genetic code, and

(d) complements of (a), (b) or (c).

In certain embodiments, the isolated nucleic acid molecule comprises one or more of nucleotides 1-1212 of SEQ ID NO:1; nucleotides 1-739 of SEQ ID NO:3; nucleotides 1-1579 of SEQ ID NO:5; nucleotides 1-5117 of SEQ ID NO:23; the mouse homolog for SOC-2/CRAC-1 corresponding to SEQ ID NO:7; nucleotides 1-2180 of SEQ ID NO:25; nucleotides 382-5976 of SEQ ID NO:27; nucleotides 73-3714 of SEQ ID NO:29; and nucleotides 23-3434 of SEQ ID NO:31. In yet other embodiments, the isolated nucleic acid molecule comprises a molecule which encodes a polypeptide having one or more sequences selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32.

According to yet another aspect of the invention, an isolated nucleic acid molecule is provided which is selected from the group consisting of:

(a) a unique fragment of a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, (of sufficient length to represent a sequence unique within the human genome); and (b) complements of (a), provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to a sequence in the prior art as represented by the sequence group consisting of: (1) sequences having the SEQ ID NOs or GenBank accession numbers of Table I, (2) complements of (1), and (3) fragments of (1) and (2).

In some embodiments, the sequence of contiguous nucleotides is selected from the group consisting of (1) at least two contiguous nucleotides nonidentical to the sequence group, (2) at least three contiguous nucleotides nonidentical to the sequence group, (3) at least four contiguous nucleotides nonidentical to the sequence group, (4) at least five contiguous nucleotides nonidentical to the sequence group, (5) at least six contiguous nucleotides nonidentical to the sequence group, (6) at least seven contiguous nucleotides nonidentical to the sequence group.

In other embodiments, the unique fragment has a size selected from the group consisting of at least: 8 nucleotides, 10 nucleotides, 12 nucleotides, 14 nucleotides, 16 nucleotides, 18 nucleotides, 20, nucleotides, 22 nucleotides, 24 nucleotides, 26 nucleotides, 28 nucleotides, 30 nucleotides, 40 nucleotides, 50 nucleotides, 75 nucleotides, 100 nucleotides, 200 nucleotides, 1000 nucleotides and every integer length therebetween.

According to another aspect of the invention, expression vectors and host cells containing (e.g., transformed or transfected with) expression vectors comprising the nucleic acid molecules disclosed herein operably linked to a promoter are provided. In certain preferred embodiments, the host cells are eukaryotic cells.

The isolated nucleic acid molecules disclosed herein have various utilities, including their use as probes and primers to identify additional members of the SOC/CRAC family of calcium channels, as diagnostic reagents for identifying the presence of SOC/CRAC polypeptides in biological or other samples, and as agents for generating SOC/CRAC binding polypeptides (e.g., antibodies) that can be used as reagents in diagnostic and therapeutic assays to identify the presence, absence, and/or amounts of a SOC/CRAC nucleic acid or polypeptide in a biological or other sample.

As used herein with respect to nucleic acids, the term "isolated" means: (i) amplified *in vitro* by, for example, polymerase chain reaction (PCR); (ii) recombinantly produced by cloning; (iii) purified, as by cleavage and gel separation; or (iv) synthesized by, for example, chemical synthesis. An isolated nucleic acid is one which is readily manipulatable by recombinant DNA techniques well known in the art. Thus, a nucleotide sequence contained in a vector in which 5' and 3' restriction sites are known or for which polymerase chain reaction (PCR) primer sequences have been disclosed is considered isolated but a nucleic acid sequence existing in its native state in its natural host is not. An isolated nucleic acid may be substantially purified, but need not be. For example, a nucleic acid that is isolated within a cloning or expression vector is not pure in that it may comprise only a tiny percentage of the

material in the cell in which it resides. Such a nucleic acid is isolated, however, as the term is used herein because it is readily manipulatable by standard techniques known to those of ordinary skill in the art.

As used herein with respect to polypeptides (discussed below), the term "isolated" means separated from its native environment in sufficiently pure form so that it can be manipulated or used for any one of the purposes of the invention. Thus, isolated means sufficiently pure to be used (i) to raise and/or isolate antibodies, (ii) as a reagent in an assay, or (iii) for sequencing, etc.

Homologs and alleles of the SOC/CRAC nucleic acids of the invention can be identified by conventional techniques. Thus, an aspect of the invention is those nucleic acid sequences which code for SOC/CRAC polypeptides and which hybridize to a nucleic acid molecule selected from a group consisting of the nucleic acid of SEQ ID NO:1, the nucleic acid of SEQ ID NO:3, the nucleic acid of SEQ ID NO:5, the nucleic acid of SEQ ID NO:7, the nucleic acid of SEQ ID NO:23, the nucleic acid of SEQ ID NO:25, the nucleic acid of SEQ ID NO:27, the nucleic acid of SEQ ID NO:29, and the nucleic acid of SEQ ID NO:31, under stringent conditions. The term "stringent conditions" as used herein refers to parameters with which the art is familiar. Nucleic acid hybridization parameters may be found in references which compile such methods, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. More specifically, stringent conditions, as used herein, refers, for example, to hybridization at 65°C in hybridization buffer (3.5 x SSC, 0.02% Ficoll, 0.02% polyvinyl pyrolidone, 0.02% Bovine Serum Albumin, 2.5mM NaH_2PO_4(pH7), 0.5% SDS, 2mM EDTA). SSC is 0.15M sodium chloride/0.15M sodium citrate, pH7; SDS is sodium dodecyl sulphate; and EDTA is ethylenediaminetetracetic acid. After hybridization, the membrane upon which the DNA is transferred is washed at 2 x SSC at room temperature and then at 0.1 x SSC/0.1 x SDS at temperatures up to 68°C.

There are other conditions, reagents, and so forth which can be used, and would result in a similar degree of stringency. The skilled artisan will be familiar with such conditions, and thus they are not given here. It will be understood, however, that the skilled artisan will be able to manipulate the conditions in a manner to permit the clear identification of homologs and alleles of the SOC/CRAC nucleic acids of the invention. The skilled artisan also is familiar with the methodology for screening cells and libraries for expression of such

molecules which then are routinely isolated, followed by isolation of the pertinent nucleic acid molecule and sequencing.

In general homologs and alleles typically will share at least 40% nucleotide identity and/or at least 50% amino acid identity to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and/or SEQ ID NO:31, and SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and/or SEQ ID NO:32, respectively. In some instances sequences will share at least 50% nucleotide identity and/or at least 65% amino acid identity and in still other instances sequences will share at least 60% nucleotide identity and/or at least 75% amino acid identity. The homology can be calculated using various, publicly available software tools developed by NCBI (Bethesda, Maryland) that can be obtained through the internet (ftp:/ncbi.nlm.nih.gov/pub/). Exemplary tools include the BLAST system available at http://www.ncbi.nlm.nih.gov. Pairwise and ClustalW alignments (BLOSUM30 matrix setting) as well as Kyte-Doolittle hydropathic analysis can be obtained using the MacVetor sequence analysis software (Oxford Molecular Group). Watson-Crick complements of the foregoing nucleic acids also are embraced by the invention.

In screening for SOC/CRAC related genes, such as homologs and alleles of SOC-2/CRAC-1 and/or SOC-3/CRAC-2, a Southern blot may be performed using the foregoing conditions, together with a radioactive probe. After washing the membrane to which the DNA is finally transferred, the membrane can be placed against X-ray film or a phosphoimager plate to detect the radioactive signal.

Given that the expression of the SOC/CRAC gene is prominent in certain human tissues (e.g., SOC-2/CRAC-1: lymphoid tissue/heart, SOC-3/CRAC-2: kidney/colon, SOC-4/CRAC-3: prostate), and given the teachings herein of partial human SOC/CRAC cDNA clones, full-length and other mammalian sequences corresponding to the human SOC/CRAC partial nucleic acid sequences can be isolated from, for example, a cDNA library prepared from one or more of the tissues in which SOC-2/CRAC-1 expression is prominent, SOC-3/CRAC-2 is prominent, and/or SOC-4/CRAC-3 expression is prominent, using standard colony hybridization techniques.

The invention also includes degenerate nucleic acids which include alternative codons to those present in the native materials. For example, serine residues are encoded by the codons TCA, AGT, TCC, TCG, TCT and AGC. Each of the six codons is equivalent for the purposes of encoding a serine residue. Thus, it will be apparent to one of ordinary skill in the

art that any of the serine-encoding nucleotide triplets may be employed to direct the protein synthesis apparatus, *in vitro* or *in vivo*, to incorporate a serine residue into an elongating SOC/CRAC polypeptide. Similarly, nucleotide sequence triplets which encode other amino acid residues include, but are not limited to: CCA, CCC, CCG and CCT (proline codons); CGA, CGC, CGG, CGT, AGA and AGG (arginine codons); ACA, ACC, ACG and ACT (threonine codons); AAC and AAT (asparagine codons); and ATA, ATC and ATT (isoleucine codons). Other amino acid residues may be encoded similarly by multiple nucleotide sequences. Thus, the invention embraces degenerate nucleic acids that differ from the biologically isolated nucleic acids in codon sequence due to the degeneracy of the genetic code.

The invention also provides isolated unique fragments of an isolated nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31. A unique fragment is one that is a 'signature' for the larger nucleic acid. For example, the unique fragment is long enough to assure that its precise sequence is not found in molecules within the human genome outside of the SOC/CRAC nucleic acids defined above (and human alleles). Those of ordinary skill in the art may apply no more than routine procedures to determine if a fragment is unique within the human genome.

Unique fragments, however, exclude fragments completely composed of the nucleotide sequences of any of GenBank accession numbers and SEQ ID NOs listed in Table I (SEQ ID NO:9, AB001535, AI226731, H18835, AA419592, AA261842, AA419407, AI098310, AA592910, D86107, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, AC005538, AA654650, AA370110, AA313170, AA493512, AI670079, AI671853, AC005538, AA654650, AA370110, AA313170, AA493512, AI670079, AI671853), or other previously published sequences as of the filing date of this application.

A fragment which is completely composed of the sequence described in the foregoing GenBank deposits and SEQ ID NO:9, is one which does not include any of the nucleotides unique to the sequences of the invention. Thus, a unique fragment must contain a nucleotide sequence other than the exact sequence of those in GenBank or fragments thereof. The difference may be an addition, deletion or substitution with respect to the GenBank sequence or it may be a sequence wholly separate from the GenBank sequence.

Unique fragments can be used as probes in Southern and Northern blot assays to identify such nucleic acids, or can be used in amplification assays such as those employing PCR. As known to those skilled in the art, large probes such as 200, 250, 300 or more nucleotides are preferred for certain uses such as Southern and Northern blots, while smaller fragments will be preferred for uses such as PCR. Unique fragments also can be used to produce fusion proteins for generating antibodies or determining binding of the polypeptide fragments, as demonstrated in the Examples, or for generating immunoassay components. Likewise, unique fragments can be employed to produce nonfused fragments of the SOC/CRAC polypeptides, useful, for example, in the preparation of antibodies, immunoassays or therapeutic applications. Unique fragments further can be used as antisense molecules to inhibit the expression of SOC/CRAC nucleic acids and polypeptides, respectively.

As will be recognized by those skilled in the art, the size of the unique fragment will depend upon its conservancy in the genetic code. Thus, some regions of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, and complements thereof, will require longer segments to be unique while others will require only short segments, typically between 12 and 32 nucleotides long (e.g. 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 and 32 bases) or more, up to the entire length of the disclosed sequence. As mentioned above, this disclosure intends to embrace each and every fragment of each sequence, beginning at the first nucleotide, the second nucleotide and so on, up to 8 nucleotides short of the end, and ending anywhere from nucleotide number 8, 9, 10 and so on for each sequence, up to the very last nucleotide, (provided the sequence is unique as described above). Virtually any segment of the region of SEQ ID NO:1 beginning at nucleotide 1 and ending at nucleotide 1212, or SEQ ID NO:3 beginning at nucleotide 1 and ending at nucleotide 739, or SEQ ID NO:5 beginning at nucleotide 1 and ending at nucleotide 1579, or SEQ ID NO:7 beginning at nucleotide 1 and ending at nucleotide 3532, or SEQ ID NO:23 beginning at nucleotide 1 and ending at nucleotide 5117, SEQ ID NO:25 beginning at nucleotide 1 and ending at nucleotide 2180, SEQ ID NO:27 beginning at nucleotide 1 and ending at nucleotide 7419, or SEQ ID NO:29 beginning at nucleotide 1 and ending at nucleotide 4061, or SEQ ID NO:31 beginning at nucleotide 1 and ending at nucleotide 4646, or complements thereof, that is 20 or more nucleotides in length will be unique. Those skilled in the art are well versed in methods for selecting such sequences, typically on the basis of the ability of the unique

fragment to selectively distinguish the sequence of interest from other sequences in the human genome of the fragment to those on known databases typically is all that is necessary, although *in vitro* confirmatory hybridization and sequencing analysis may be performed.

As mentioned above, the invention embraces antisense oligonucleotides that selectively bind to a nucleic acid molecule encoding a SOC/CRAC polypeptide, to decrease SOC/CRAC calcium channel activity. When using antisense preparations of the invention, slow intravenous administration is preferred.

As used herein, the term "antisense oligonucleotide" or "antisense" describes an oligonucleotide that is an oligoribonucleotide, oligodeoxyribonucleotide, modified oligoribonucleotide, or modified oligodeoxyribonucleotide which hybridizes under physiological conditions to DNA comprising a particular gene or to an mRNA transcript of that gene and, thereby, inhibits the transcription of that gene and/or the translation of that mRNA. The antisense molecules are designed so as to interfere with transcription or translation of a target gene upon hybridization with the target gene or transcript. Those skilled in the art will recognize that the exact length of the antisense oligonucleotide and its degree of complementarity with its target will depend upon the specific target selected, including the sequence of the target and the particular bases which comprise that sequence. It is preferred that the antisense oligonucleotide be constructed and arranged so as to bind selectively with the target under physiological conditions, i.e., to hybridize substantially more to the target sequence than to any other sequence in the target cell under physiological conditions. Based upon SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, or upon allelic or homologous genomic and/or cDNA sequences, one of skill in the art can easily choose and synthesize any of a number of appropriate antisense molecules for use in accordance with the present invention. In order to be sufficiently selective and potent for inhibition, such antisense oligonucleotides should comprise at least 10 and, more preferably, at least 15 consecutive bases which are complementary to the target, although in certain cases modified oligonucleotides as short as 7 bases in length have been used successfully as antisense oligonucleotides (Wagner et al., *Nat. Med.* 1(11):1116-1118, 1995). Most preferably, the antisense oligonucleotides comprise a complementary sequence of 20-30 bases. Although oligonucleotides may be chosen which are antisense to any region of the gene or mRNA transcripts, in preferred embodiments the antisense oligonucleotides correspond to N-terminal or 5' upstream sites such as translation initiation, transcription initiation or promoter sites. In

addition, 3'-untranslated regions may be targeted by antisense oligonucleotides. Targeting to mRNA splicing sites has also been used in the art but may be less preferred if alternative mRNA splicing occurs. In addition, the antisense is targeted, preferably, to sites in which mRNA secondary structure is not expected (see, e.g., Sainio et al., *Cell Mol. Neurobiol.* 14(5):439-457, 1994) and at which proteins are not expected to bind. Finally, although, SEQ ID No:1 discloses a cDNA sequence, one of ordinary skill in the art may easily derive the genomic DNA corresponding to this sequence. Thus, the present invention also provides for antisense oligonucleotides which are complementary to the genomic DNA corresponding to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5,SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31. Similarly, antisense to allelic or homologous SOC/CRAC cDNAs and genomic DNAs are enabled without undue experimentation.

In one set of embodiments, the antisense oligonucleotides of the invention may be composed of "natural" deoxyribonucleotides, ribonucleotides, or any combination thereof. That is, the 5' end of one native nucleotide and the 3' end of another native nucleotide may be covalently linked, as in natural systems, via a phosphodiester internucleoside linkage. These oligonucleotides may be prepared by art recognized methods which may be carried out manually or by an automated synthesizer. They also may be produced recombinantly by vectors.

In preferred embodiments, however, the antisense oligonucleotides of the invention also may include "modified" oligonucleotides. That is, the oligonucleotides may be modified in a number of ways which do not prevent them from hybridizing to their target but which enhance their stability or targeting or which otherwise enhance their therapeutic effectiveness.

The term "modified oligonucleotide" as used herein describes an oligonucleotide in which (1) at least two of its nucleotides are covalently linked via a synthetic internucleoside linkage (i.e., a linkage other than a phosphodiester linkage between the 5' end of one nucleotide and the 3' end of another nucleotide) and/or (2) a chemical group not normally associated with nucleic acids has been covalently attached to the oligonucleotide. Preferred synthetic internucleoside linkages are phosphorothioates, alkylphosphonates, phosphorodithioates, phosphate esters, alkylphosphonothioates, phosphoramidates, carbamates, carbonates, phosphate triesters, acetamidates, carboxymethyl esters and peptides.

The term "modified oligonucleotide" also encompasses oligonucleotides with a covalently modified base and/or sugar. For example, modified oligonucleotides include

oligonucleotides having backbone sugars which are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 3' position and other than a phosphate group at the 5' position. Thus modified oligonucleotides may include a 2'-O-alkylated ribose group. In addition, modified oligonucleotides may include sugars such as arabinose instead of ribose. The present invention, thus, contemplates pharmaceutical preparations containing modified antisense molecules that are complementary to and hybridizable with, under physiological conditions, nucleic acids encoding SOC/CRAC polypeptides, together with pharmaceutically acceptable carriers. Antisense oligonucleotides may be administered as part of a pharmaceutical composition. Such a pharmaceutical composition may include the antisense oligonucleotides in combination with any standard physiologically and/or pharmaceutically acceptable carriers which are known in the art. The compositions should be sterile and contain a therapeutically effective amount of the antisense oligonucleotides in a unit of weight or volume suitable for administration to a patient. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients. The term "physiologically acceptable" refers to a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism. The characteristics of the carrier will depend on the route of administration. Physiologically and pharmaceutically acceptable carriers include diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials which are well known in the art.

The invention also involves expression vectors coding for SOC/CRAC proteins and fragments and variants thereof and host cells containing those expression vectors. Virtually any cells, prokaryotic or eukaryotic, which can be transformed with heterologous DNA or RNA and which can be grown or maintained in culture, may be used in the practice of the invention. Examples include bacterial cells such as E.coli and eukaryotic cells such as mouse, hamster, pig, goat, primate, yeast, xenopous, etc. They may be of a wide variety of tissue types, including mast cells, fibroblasts, oocytes and lymphocytes, and they may be primary cells or cell lines. Specific examples include CHO cells and COS cells. Cell-free transcription systems also may be used in lieu of cells.

As used herein, a "vector" may be any of a number of nucleic acids into which a desired sequence may be inserted by restriction and ligation for transport between different genetic environments or for expression in a host cell. Vectors are typically composed of DNA although RNA vectors are also available. Vectors include, but are not limited to,

plasmids, phagemids and virus genomes. A cloning vector is one which is able to replicate in a host cell, and which is further characterized by one or more endonuclease restriction sites at which the vector may be cut in a determinable fashion and into which a desired DNA sequence may be ligated such that the new recombinant vector retains its ability to replicate in the host cell. In the case of plasmids, replication of the desired sequence may occur many times as the plasmid increases in copy number within the host bacterium or just a single time per host before the host reproduces by mitosis. In the case of phage, replication may occur actively during a lytic phase or passively during a lysogenic phase. An expression vector is one into which a desired DNA sequence may be inserted by restriction and ligation such that it is operably joined to regulatory sequences and may be expressed as an RNA transcript. Vectors may further contain one or more marker sequences suitable for use in the identification of cells which have or have not been transformed or transfected with the vector. Markers include, for example, genes encoding proteins which increase or decrease either resistance or sensitivity to antibiotics or other compounds, genes which encode enzymes whose activities are detectable by standard assays known in the art (e.g., β-galactosidase or alkaline phosphatase), and genes which visibly affect the phenotype of transformed or transfected cells, hosts, colonies or plaques (e.g., green fluorescent protein). Preferred vectors are those capable of autonomous replication and expression of the structural gene products present in the DNA segments to which they are operably joined.

As used herein, a coding sequence and regulatory sequences are said to be "operably" joined when they are covalently linked in such a way as to place the expression or transcription of the coding sequence under the influence or control of the regulatory sequences. If it is desired that the coding sequences be translated into a functional protein, two DNA sequences are said to be operably joined if induction of a promoter in the 5' regulatory sequences results in the transcription of the coding sequence and if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter region to direct the transcription of the coding sequences, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. Thus, a promoter region would be operably joined to a coding sequence if the promoter region were capable of effecting transcription of that DNA sequence such that the resulting transcript might be translated into the desired protein or polypeptide.

The precise nature of the regulatory sequences needed for gene expression may vary between species or cell types, but shall in general include, as necessary, 5' non-transcribed

and 5' non-translated sequences involved with the initiation of transcription and translation respectively, such as a TATA box, capping sequence, CAAT sequence, and the like. Especially, such 5' non-transcribed regulatory sequences will include a promoter region which includes a promoter sequence for transcriptional control of the operably joined gene. Regulatory sequences may also include enhancer sequences or upstream activator sequences as desired. The vectors of the invention may optionally include 5' leader or signal sequences. The choice and design of an appropriate vector is within the ability and discretion of one of ordinary skill in the art.

According to yet another aspect of the invention, isolated SOC/CRAC polypeptides are provided. Preferably, the isolated SOC/CRAC polypeptides are encoded by the isolated SOC/CRAC nucleic acid molecules disclosed herein. More preferably, the isolated SOC/CRAC polypeptides of the invention are encoded by the nucleic acid molecules having SEQ ID Nos. 1, 3, 5, 7, 23, 25, 27, 29, and 31. In yet other embodiments, the isolated SOC/CRAC polypeptides of the invention have an amino acid sequence selected from the group consisting of SEQ ID Nos. 2, 4, 6, 8, 24, 26, 28, 30 and 32. Preferably, the isolated SOC/CRAC polypeptides are of sufficient length to represent a sequence unique within the human genome. Thus, the preferred embodiments include a sequence of contiguous amino acids which is not identical to a prior art sequence as represented by the sequence group consisting of the contiguous amino acids identified in Table II (SEQ ID NO:10, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19 and GenBank Acc. Nos. AB001535, AA592910, D86107, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, NP003298, CAB00861, NP002411, CAA92726, CAB05572).

In certain embodiments, the isolated SOC/CRAC polypeptides are immunogenic and can be used to generate binding polypeptides (e.g., antibodies) for use in diagnostic and therapeutic applications. Such binding polypeptides also are useful for detecting the presence, absence, and/or amounts of a SOC/CRAC nucleic acid or polypeptide in a sample such as a biological fluid or biopsy sample. Preferably, the SOC/CRAC polypeptides that are useful for generating binding polypeptides are unique polypeptides and, therefore, binding of the antibody to a SOC/CRAC polypeptide in a sample is selective for the SOC/CRAC polypeptide.

Expression vectors containing all the necessary elements for expression are commercially available and known to those skilled in the art. See, e.g., Sambrook et al.,

Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989. Cells are genetically engineered by the introduction into the cells of heterologous DNA (RNA) encoding a SOC/CRAC polypeptide or fragment or variant thereof. The heterologous DNA (RNA) is placed under operable control of transcriptional elements to permit the expression of the heterologous DNA in the host cell.

Preferred systems for mRNA expression in mammalian cells are those such as pRc/CMV (available from Invitrogen, Carlsbad, CA) that contain a selectable marker such as a gene that confers G418 resistance (which facilitates the selection of stably transfected cell lines) and the human cytomegalovirus (CMV) enhancer-promoter sequences. Additionally, suitable for expression in primate or canine cell lines is the pCEP4 vector (Invitrogen, Carlsbad, CA), which contains an Epstein Barr virus (EBV) origin of replication, facilitating the maintenance of plasmid as a multicopy extrachromosomal element. Another expression vector is the pEF-BOS plasmid containing the promoter of polypeptide Elongation Factor 1α, which stimulates efficiently transcription *in vitro*. The plasmid is described by Mishizuma and Nagata (*Nuc. Acids Res.* 18:5322, 1990), and its use in transfection experiments is disclosed by, for example, Demoulin (*Mol. Cell. Biol.* 16:4710-4716, 1996). Still another preferred expression vector is an adenovirus, described by Stratford-Perricaudet, which is defective for E1 and E3 proteins (*J. Clin. Invest.* 90:626-630, 1992). The use of the adenovirus as an Adeno.P1A recombinant is disclosed by Warnier et al., in intradermal injection in mice for immunization against P1A (*Int. J. Cancer*, 67:303-310, 1996).

The invention also embraces so-called expression kits, which allow the artisan to prepare a desired expression vector or vectors. Such expression kits include at least separate portions of each of the previously discussed coding sequences. Other components may be added, as desired, as long as the previously mentioned sequences, which are required, are included.

It will also be recognized that the invention embraces the use of the above described, SOC/CRAC cDNA sequence containing expression vectors, to transfect host cells and cell lines, by these prokaryotic (e.g., E. coli), or eukaryotic (e.g., CHO cells, COS cells, yeast expression systems and recombinant baculovirus expression in insect cells). Especially useful are mammalian cells such as mouse, hamster, pig, goat, primate, etc. They may be of a wide variety of tissue types, and include primary cells and cell lines. Specific examples include dendritic cells, U293 cells, peripheral blood leukocytes, bone marrow stem cells and embryonic stem cells. The invention also permits the construction of SOC/CRAC gene

"knock-outs" in cells and in animals, providing materials for studying certain aspects of SOC/CRAC calcium channel activity.

The invention also provides isolated polypeptides (including whole proteins and partial proteins), encoded by the foregoing SOC/CRAC nucleic acids, and include the polypeptides of SEQ ID NO:2, 4, 6, 8, 24, 26, 28, 30, 32, and unique fragments thereof. Such polypeptides are useful, for example, to regulate calcium transport-mediated cell growth, differentiation and proliferation, to generate antibodies, as components of immunoassays, etc. Polypeptides can be isolated from biological samples including tissue or cell homogenates, and can also be expressed recombinantly in a variety of prokaryotic and eukaryotic expression systems by constructing an expression vector appropriate to the expression system, introducing the expression vector into the expression system, and isolating the recombinantly expressed protein. Short polypeptides, including antigenic peptides (such as are presented by MHC molecules on the surface of a cell for immune recognition) also can be synthesized chemically using well-established methods of peptide synthesis.

A unique fragment of a SOC/CRAC polypeptide, in general, has the features and characteristics of unique fragments as discussed above in connection with nucleic acids. As will be recognized by those skilled in the art, the size of the unique fragment will depend upon factors such as whether the fragment constitutes a portion of a conserved protein domain. Thus, some regions of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and/or SEQ ID NO:32, will require longer segments to be unique while others will require only short segments, typically between 5 and 12 amino acids (e.g. 5, 6, 7, 8, 9, 10, 11 and 12 amino acids long or more, including each integer up to the full length, >1,000 amino acids long). Virtually any segment of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and/or SEQ ID NO:32, excluding the ones that share identity with it (the polypeptides identified in Table II - SEQ ID NO:10, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, and GenBank Acc. Nos. AB001535, AA592910, D86107, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, NP003298, CAB00861, NP002411, CAA92726, CAB05572) that is 9 or more amino acids in length will be unique.

Unique fragments of a polypeptide preferably are those fragments which retain a distinct functional capability of the polypeptide. Functional capabilities which can be retained in a unique fragment of a polypeptide include Ca^{2+} fluxing, high selectivity, a unitary

conductance below the detection level of the patch clamp method, and/or and are subject to inhibition by high intracellular calcium levels.

One important aspect of a unique fragment is its ability to act as a signature for identifying the polypeptide. Optionally, another aspect of a unique fragment is its ability to provide an immune response in an animal. Those skilled in the art are well versed in methods for selecting unique amino acid sequences, typically on the basis of the ability of the unique fragment to selectively distinguish the sequence of interest from non-family members. A comparison of the sequence of the fragment to those on known databases typically is all that is necessary.

The invention embraces variants of the SOC/CRAC polypeptides described above. As used herein, a "variant" of a SOC/CRAC polypeptide is a polypeptide which contains one or more modifications to the primary amino acid sequence of a SOC/CRAC polypeptide. Modifications which create a SOC/CRAC polypeptide variant are typically made to the nucleic acid which encodes the SOC/CRAC polypeptide, and can include deletions, point mutations, truncations, amino acid substitutions and addition of amino acids or non-amino acid moieties to: 1) reduce or eliminate a calcium channel activity of a SOC/CRAC polypeptide; 2) enhance a property of a SOC/CRAC polypeptide, such as protein stability in an expression system or the stability of protein-protein binding; 3) provide a novel activity or property to a SOC/CRAC polypeptide, such as addition of an antigenic epitope or addition of a detectable moiety; or 4) to provide equivalent or better binding to a SOC/CRAC polypeptide receptor or other molecule. Alternatively, modifications can be made directly to the polypeptide, such as by cleavage, addition of a linker molecule, addition of a detectable moiety, such as biotin, addition of a fatty acid, and the like. Modifications also embrace fusion proteins comprising all or part of the SOC/CRAC amino acid sequence. One of skill in the art will be familiar with methods for predicting the effect on protein conformation of a change in protein sequence, and can thus "design" a variant SOC/CRAC polypeptide according to known methods. One example of such a method is described by Dahiyat and Mayo in *Science* 278:82-87, 1997, whereby proteins can be designed *de novo*. The method can be applied to a known protein to vary only a portion of the polypeptide sequence. By applying the computational methods of Dahiyat and Mayo, specific variants of a SOC/CRAC calcium channel polypeptide can be proposed and tested to determine whether the variant retains a desired conformation.

Variants can include SOC/CRAC polypeptides which are modified specifically to alter a feature of the polypeptide unrelated to its physiological activity. For example, cysteine residues can be substituted or deleted to prevent unwanted disulfide linkages. Similarly, certain amino acids can be changed to enhance expression of a SOC/CRAC polypeptide by eliminating proteolysis by proteases in an expression system (e.g., dibasic amino acid residues in yeast expression systems in which KEX2 protease activity is present).

Mutations of a nucleic acid which encodes a SOC/CRAC polypeptide preferably preserve the amino acid reading frame of the coding sequence and, preferably, do not create regions in the nucleic acid which are likely to hybridize to form secondary structures, such as hairpins or loops, which can be deleterious to expression of the variant polypeptide.

Mutations can be made by selecting an amino acid substitution, or by random mutagenesis of a selected site in a nucleic acid which encodes the polypeptide. Variant polypeptides are then expressed and tested for one or more activities to determine which mutation provides a variant polypeptide with the desired properties. Further mutations can be made to variants (or to non-variant SOC/CRAC polypeptides) which are silent as to the amino acid sequence of the polypeptide, but which provide preferred codons for translation in a particular host. The preferred codons for translation of a nucleic acid in, e.g., E. coli, are well known to those of ordinary skill in the art. Still other mutations can be made to the noncoding sequences of a SOC/CRAC gene or cDNA clone to enhance expression of the polypeptide.

The skilled artisan will realize that conservative amino acid substitutions may be made in SOC/CRAC polypeptides to provide functionally equivalent variants of the foregoing polypeptides, i.e, the variants retain the functional capabilities of the SOC/CRAC polypeptides. As used herein, a "conservative amino acid substitution" refers to an amino acid substitution which does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Variants can be prepared according to methods for altering polypeptide sequence known to one of ordinary skill in the art such as are found in references which compile such methods, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. Exemplary functionally equivalent variants of the SOC/CRAC polypeptides include conservative amino acid substitutions of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and/or SEQ ID NO:32. Conservative substitutions of amino acids

include substitutions made amongst amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q, N; and (g) E, D.

Thus functionally equivalent variants of SOC/CRAC polypeptides, i.e., variants of SOC/CRAC polypeptides which retain the function of the natural SOC/CRAC polypeptides, are contemplated by the invention. Conservative amino-acid substitutions in the amino acid sequence of SOC/CRAC polypeptides to produce functionally equivalent variants of SOC/CRAC polypeptides typically are made by alteration of a nucleic acid encoding SOC/CRAC polypeptides (e.g., SEQ ID NOs:1, 3, 5, 7, 23, 25, 27, 29, 31). Such substitutions can be made by a variety of methods known to one of ordinary skill in the art. For example, amino acid substitutions may be made by PCR-directed mutation, site-directed mutagenesis according to the method of Kunkel (Kunkel, *Proc. Nat. Acad. Sci. U.S.A.* 82: 488-492, 1985), or by chemical synthesis of a gene encoding a SOC/CRAC polypeptide. The activity of functionally equivalent fragments of SOC/CRAC polypeptides can be tested by cloning the gene encoding the altered SOC/CRAC polypeptide into a bacterial or mammalian expression vector, introducing the vector into an appropriate host cell, expressing the altered SOC/CRAC polypeptide, and testing for a functional capability of the SOC/CRAC polypeptides as disclosed herein (e.g., SOC/CRAC calcium channel activity).

The invention as described herein has a number of uses, some of which are described elsewhere herein. First, the invention permits isolation of SOC/CRAC polypeptides, including the isolation of the complete SOC/CRAC polypeptide. A variety of methodologies well-known to the skilled practitioner can be utilized to obtain isolated SOC/CRAC molecules. The polypeptide may be purified from cells which naturally produce the polypeptide by chromatographic means or immunological recognition. Alternatively, an expression vector may be introduced into cells to cause production of the polypeptide. In another method, mRNA transcripts may be microinjected or otherwise introduced into cells to cause production of the encoded polypeptide. Translation of SOC/CRAC mRNA in cell-free extracts such as the reticulocyte lysate system also may be used to produce SOC/CRAC polypeptides. Those skilled in the art also can readily follow known methods for isolating SOC/CRAC polypeptides. These include, but are not limited to, immunochromatography, HPLC, size-exclusion chromatography, ion-exchange chromatography and immune-affinity chromatography.

The invention also provides, in certain embodiments, "dominant negative" polypeptides derived from SOC/CRAC polypeptides. A dominant negative polypeptide is an

inactive variant of a protein, which, by interacting with the cellular machinery, displaces an active protein from its interaction with the cellular machinery or competes with the active protein, thereby reducing the effect of the active protein. For example, a dominant negative receptor which binds a ligand but does not transmit a signal in response to binding of the ligand can reduce the biological effect of expression of the ligand. Likewise, a dominant negative inactive SOC/CRAC calcium channel which interacts normally with the cell membrane but which does not mediate calcium transport can reduce calcium transport in a cell. Similarly, a dominant negative transcription factor which binds to a promoter site in the control region of a gene but does not increase gene transcription can reduce the effect of a normal transcription factor by occupying promoter binding sites without increasing transcription.

The end result of the expression of a dominant negative polypeptide in a cell is a reduction in function of active proteins. One of ordinary skill in the art can assess the potential for a dominant negative variant of a protein, and using standard mutagenesis techniques to create one or more dominant negative variant polypeptides. See, e.g., U.S. Patent No. 5,580,723 and Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press. The skilled artisan then can test the population of mutagenized polypeptides for diminution in a selected and/or for retention of such an activity. Other similar methods for creating and testing dominant negative variants of a protein will be apparent to one of ordinary skill in the art.

According to another aspect, the invention provides a method for isolating a SOC/CRAC molecule having SOC/CRAC calcium channel activity. The method involves contacting a binding molecule that is a SOC/CRAC nucleic acid or a SOC/CRAC binding polypeptide with a sample containing one or more SOC/CRAC molecules under conditions that allow such binding (see earlier discussion) to form a complex, detecting the presence of the complex, isolating the SOC/CRAC molecule from the complex, and determining whether the isolated SOC/CRAC molecule has SOC/CRAC calcium channel activity. Thus, the invention is useful for identifying and isolating full length complementary (cDNA) or genomic nucleic acids encoding SOC/CRAC polypeptides having SOC/CRAC calcium channel activity. Identification and isolation of such nucleic acids and polypeptides may be accomplished by hybridizing/binding, under appropriate conditions well known in the art, libraries and/or restriction enzyme-digested human nucleic acids, with a labeled SOC/CRAC molecular probe. As used herein, a "label" includes molecules that are incorporated into, for

example, a SOC/CRAC molecule (nucleic acid or peptide), that can be directly or indirectly detected. A wide variety of detectable labels are well known in the art that can be used, and include labels that provide direct detection (e.g., radioactivity, luminescence, optical or electron density, etc), or indirect detection (e.g., epitope tag such as the FLAG epitope, enzyme tag such as horseseradish peroxidase, etc.). The label may be bound to a SOC/CRAC binding partner, or incorporated into the structure of the binding partner.

A variety of methods may be used to detect the label, depending on the nature of the label and other assay components. For example, the label may be detected while bound to the solid substrate or subsequent to separation from the solid substrate. Labels may be directly detected through optical or electron density, radioactive emissions, nonradioactive energy transfers, etc. or indirectly detected with antibody conjugates, strepavidin-biotin conjugates, etc. Methods for detecting the labels are well known in the art. Once a library clone or hybridizing fragment is identified in the hybridization/binding reaction, it can be further isolated by employing standard isolation/cloning techniques known to those of skill in the art. See, generally, Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*, 2nd Edition, Cold Spring Harbor Laboratory Press. In addition, nucleic acid amplification techniques well known in the art, may also be used to locate splice variants of calcium channel (or calcium channel subunits) with SOC/CRAC calcium channel activity. Size and sequence determinations of the amplification products can reveal splice variants.

The foregoing isolated nucleic acids and polypeptides may then be compared to the nucleic acids and polypeptides of the present invention in order to identify homogeneity or divergence of the sequences, and be further characterized functionally to determine whether they belong to a family of molecules with SOC/CRAC calcium channel activity (for methodology see under the Examples section).

The isolation of the SOC/CRAC cDNA and/or partial sequences thereof also makes it possible for the artisan to diagnose a disorder characterized by an aberrant expression of SOC/CRAC. These methods involve determining expression of the SOC/CRAC gene, and/or SOC/CRAC polypeptides derived therefrom. In the former situation, such determinations can be carried out via any standard nucleic acid determination assay, including the polymerase chain reaction, or assaying with labeled hybridization probes as exemplified below. In the latter situation, such determination can be carried out via any standard immunological assay using, for example, antibodies which bind to the SOC/CRAC protein.

The invention also embraces isolated peptide binding agents which, for example, can be antibodies or fragments of antibodies ("binding polypeptides"), having the ability to selectively bind to SOC/CRAC polypeptides. Antibodies include polyclonal and monoclonal antibodies, prepared according to conventional methodology. In certain embodiments, the invention excludes binding agents (e.g., antibodies) that bind to the polypeptides encoded by the nucleic acids of SEQ ID NOs: 10, 12, 13, 14, 15, 17, and 19.

Significantly, as is well-known in the art, only a small portion of an antibody molecule, the paratope, is involved in the binding of the antibody to its epitope (see, in general, Clark, W.R. (1986) The Experimental Foundations of Modern Immunology Wiley & Sons, Inc., New York; Roitt, I. (1991) Essential Immunology, 7th Ed., Blackwell Scientific Publications, Oxford). The pFc' and Fc regions, for example, are effectors of the complement cascade but are not involved in antigen binding. An antibody from which the pFc' region has been enzymatically cleaved, or which has been produced without the pFc' region, designated an $F(ab')_2$ fragment, retains both of the antigen binding sites of an intact antibody. Similarly, an antibody from which the Fc region has been enzymatically cleaved, or which has been produced without the Fc region, designated an Fab fragment, retains one of the antigen binding sites of an intact antibody molecule. Proceeding further, Fab fragments consist of a covalently bound antibody light chain and a portion of the antibody heavy chain denoted Fd. The Fd fragments are the major determinant of antibody specificity (a single Fd fragment may be associated with up to ten different light chains without altering antibody specificity) and Fd fragments retain epitope-binding ability in isolation.

Within the antigen-binding portion of an antibody, as is well-known in the art, there are complementarity determining regions (CDRs), which directly interact with the epitope of the antigen, and framework regions (FRs), which maintain the tertiary structure of the paratope (see, in general, Clark, 1986; Roitt, 1991). In both the heavy chain Fd fragment and the light chain of IgG immunoglobulins, there are four framework regions (FR1 through FR4) separated respectively by three complementarity determining regions (CDR1 through CDR3). The CDRs, and in particular the CDR3 regions, and more particularly the heavy chain CDR3, are largely responsible for antibody specificity.

It is now well-established in the art that the non-CDR regions of a mammalian antibody may be replaced with similar regions of conspecific or heterospecific antibodies while retaining the epitopic specificity of the original antibody. This is most clearly manifested in the development and use of "humanized" antibodies in which non-human CDRs

are covalently joined to human FR and/or Fc/pFc' regions to produce a functional antibody. Thus, for example, PCT International Publication Number WO 92/04381 teaches the production and use of humanized murine RSV antibodies in which at least a portion of the murine FR regions have been replaced by FR regions of human origin. Such antibodies, including fragments of intact antibodies with antigen-binding ability, are often referred to as "chimeric" antibodies.

Thus, as will be apparent to one of ordinary skill in the art, the present invention also provides for $F(ab')_2$, Fab, Fv and Fd fragments; chimeric antibodies in which the Fc and/or FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric $F(ab')_2$ fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric Fab fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; and chimeric Fd fragment antibodies in which the FR and/or CDR1 and/or CDR2 regions have been replaced by homologous human or non-human sequences. The present invention also includes so-called single chain antibodies.

Thus, the invention involves binding polypeptides of numerous size and type that bind selectively to SOC/CRAC polypeptides, and complexes containing SOC/CRAC polypeptides. These binding polypeptides also may be derived also from sources other than antibody technology. For example, such polypeptide binding agents can be provided by degenerate peptide libraries which can be readily prepared in solution, in immobilized form, as bacterial flagella peptide display libraries or as phage display libraries. Combinatorial libraries also can be synthesized of peptides containing one or more amino acids. Libraries further can be synthesized of peptides and non-peptide synthetic moieties.

Phage display can be particularly effective in identifying binding peptides useful according to the invention. Briefly, one prepares a phage library (using e.g. m13, fd, or lambda phage), displaying inserts from 4 to about 80 amino acid residues using conventional procedures. The inserts may represent, for example, a completely degenerate or biased array. One then can select phage-bearing inserts which bind to the SOC/CRAC polypeptide or a complex containing a SOC/CRAC polypeptide. This process can be repeated through several cycles of reselection of phage that bind to the SOC/CRAC polypeptide or complex. Repeated rounds lead to enrichment of phage bearing particular sequences. DNA sequence analysis can be conducted to identify the sequences of the expressed polypeptides. The minimal linear

portion of the sequence that binds to the SOC/CRAC polypeptide or complex can be determined. One can repeat the procedure using a biased library containing inserts containing part or all of the minimal linear portion plus one or more additional degenerate residues upstream or downstream thereof. Yeast two-hybrid screening methods also may be used to identify polypeptides that bind to the SOC/CRAC polypeptides. Thus, the SOC/CRAC polypeptides of the invention, or a fragment thereof, or complexes of SOC/CRAC can be used to screen peptide libraries, including phage display libraries, to identify and select peptide binding polypeptides that selectively bind to the SOC/CRAC polypeptides of the invention. Such molecules can be used, as described, for screening assays, for purification protocols, for interfering directly with the functioning of SOC/CRAC and for other purposes that will be apparent to those of ordinary skill in the art.

A SOC/CRAC polypeptide, or a fragment thereof, also can be used to isolate naturally occurring, polypeptide binding partners which may associate with the SOC/CRAC polypeptide in the membrane of a cell. Isolation of binding partners may be performed according to well-known methods. For example, isolated SOC/CRAC polypeptides can be attached to a substrate, and then a solution suspected of containing an SOC/CRAC binding partner may be applied to the substrate. If the binding partner for SOC/CRAC polypeptides is present in the solution, then it will bind to the substrate-bound SOC/CRAC polypeptide. The binding partner then may be isolated. Other proteins which are binding partners for SOC/CRAC, may be isolated by similar methods without undue experimentation.

The invention also provides novel kits which could be used to measure the levels of the nucleic acids of the invention, expression products of the invention or anti-SOC/CRAC antibodies. In the case of nucleic acid detection, pairs of primers for amplifying SOC/CRAC nucleic acids can be included. The preferred kits would include controls such as known amounts of nucleic acid probes, SOC/CRAC epitopes (such as SOC/CRAC expression products) or anti-SOC/CRAC antibodies, as well as instructions or other printed material. In certain embodiments the printed material can characterize risk of developing a disorder that is characterized by aberrant SOC/CRAC polypeptide expression based upon the outcome of the assay. The reagents may be packaged in containers and/or coated on wells in predetermined amounts, and the kits may include standard materials such as labeled immunological reagents (such as labeled anti-IgG antibodies) and the like. One kit is a packaged polystyrene microtiter plate coated with a SOC/CRAC polypeptide and a container containing labeled anti-human IgG antibodies. A well of the plate is contacted with, for example, serum, washed

and then contacted with the anti-IgG antibody. The label is then detected. A kit embodying features of the present invention is comprised of the following major elements: packaging an agent of the invention, a control agent, and instructions. Packaging is a box-like structure for holding a vial (or number of vials) containing an agent of the invention. a vial (or number of vials) containing a control agent, and instructions. Individuals skilled in the art can readily modify packaging to suit individual needs.

Another aspect of the invention is a method for determining the level of SOC/CRAC expression in a subject. As used herein, a subject is a human, non-human primate, cow, horse, pig, sheep, goat, dog, cat or rodent. In all embodiments, human subjects are preferred. Expression is defined either as SOC/CRAC mRNA expression or SOC/CRAC polypeptide expression. Various methods can be used to measure expression. Preferred embodiments of the invention include PCR and Northern blotting for measuring mRNA expression, and monoclonal or polyclonal SOC/CRAC antisera as reagents to measure SOC/CRAC polypeptide expression. In certain embodiments, test samples such as biopsy samples, and biological fluids such as blood, are used as test samples. SOC/CRAC expression in a test sample of a subject is compared to SOC/CRAC expression in control sample to, e.g., assess the presence or absence or stage of a proliferative disorder (e.g., a lymphocyte proliferative disorder) in a subject.

SOC/CRAC polypeptides preferably are produced recombinantly, although such polypeptides may be isolated from biological extracts. Recombinantly produced SOC/CRAC polypeptides include chimeric proteins comprising a fusion of a SOC/CRAC protein with another polypeptide, e.g., a polypeptide capable of providing or enhancing protein-protein binding, sequence specific nucleic acid binding (such as GAL4), enhancing stability of the SOC/CRAC polypeptide under assay conditions, or providing a detectable moiety, such as green fluorescent protein. A polypeptide fused to a SOC/CRAC polypeptide or fragment may also provide means of readily detecting the fusion protein, e.g., by immunological recognition or by fluorescent labeling.

The invention is also useful in the generation of transgenic non-human animals. As used herein, "transgenic non-human animals" includes non-human animals having one or more exogenous nucleic acid molecules incorporated in germ line cells and/or somatic cells. Thus the transgenic animal include "knockout" animals having a homozygous or heterozygous gene disruption by homologous recombination, animals having episomal or chromosomally incorporated expression vectors, etc. Knockout animals can be prepared by

homologous recombination using embryonic stem cells as is well known in the art. The recombination may be facilitated using, for example, the cre/lox system or other recombinase systems known to one of ordinary skill in the art. In certain embodiments, the recombinase system itself is expressed conditionally, for example, in certain tissues or cell types, at certain embryonic or post-embryonic developmental stages, inducibly by the addition of a compound which increases or decreases expression, and the like. In general, the conditional expression vectors used in such systems use a variety of promoters which confer the desired gene expression pattern (e.g., temporal or spatial). Conditional promoters also can be operably linked to SOC/CRAC nucleic acid molecules to increase expression of SOC/CRAC in a regulated or conditional manner. *Trans*-acting negative regulators of SOC/CRAC calcium channel activity or expression also can be operably linked to a conditional promoter as described above. Such *trans*-acting regulators include antisense SOC/CRAC nucleic acids molecules, nucleic acid molecules which encode dominant negative SOC/CRAC molecules, ribozyme molecules specific for SOC/CRAC nucleic acids, and the like. The transgenic non-human animals are useful in experiments directed toward testing biochemical or physiological effects of diagnostics or therapeutics for conditions characterized by increased or decreased SOC/CRAC expression. Other uses will be apparent to one of ordinary skill in the art.

The invention further provides efficient methods of identifying agents or lead compounds for agents active at the level of a SOC/CRAC polypeptide (e.g., a SOC/CRAC polypeptide) or SOC/CRAC fragment dependent cellular function. In particular, such functions include interaction with other polypeptides or fragments thereof, and selective binding to certain molecules (e.g., agonists and antagonists). Generally, the screening methods involve assaying for compounds which interfere with SOC/CRAC calcium channel activity, although compounds which enhance SOC/CRAC calcium channel activity also can be assayed using the screening methods. Such methods are adaptable to automated, high throughput screening of compounds. The target therapeutic indications for pharmacological agents detected by the screening methods are limited only in that the target cellular function be subject to modulation by alteration of the formation of a complex comprising a SOC/CRAC polypeptide or fragment thereof and one or more SOC/CRAC binding targets. Target indications include cellular processes modulated by SOC/CRAC such as Ca^{2+} fluxing, and affected by SOC/CRAC ability to form complexes with other molecules and polypeptides as, for example, may be present in the cell membrane.

A wide variety of assays for pharmacological agents are provided, including, expression assays, labeled *in vitro* protein-protein binding assays, electrophoretic mobility shift assays, immunoassays, cell-based assays such as calcium transport assays, etc. For example, two-hybrid screens are used to rapidly examine the effect of transfected nucleic acids on the intracellular binding of SOC/CRAC or SOC/CRAC fragments to specific intracellular targets (e.g. a tyrosine kinase). The transfected nucleic acids can encode, for example, combinatorial peptide libraries or cDNA libraries. Convenient reagents for such assays, e.g., GAL4 fusion proteins, are known in the art. An exemplary cell-based assay involves transfecting a cell with a nucleic acid encoding a SOC/CRAC polypeptide fused to a GAL4 DNA binding domain and a nucleic acid encoding a reporter gene operably linked to a gene expression regulatory region, such as one or more GAL4 binding sites. Activation of reporter gene transcription occurs when the SOC/CRAC and reporter fusion polypeptides bind such as to enable transcription of the reporter gene. Agents which modulate a SOC/CRAC polypeptide mediated cell function are then detected through a change in the expression of reporter gene. Methods for determining changes in the expression of a reporter gene are known in the art.

In an expression system, for example, a SOC/CRAC polypeptide is attached to a membrane, the membrane preferably separating two fluid environments and being otherwise not permeable to Ca^{2+}. Such separation is preferred so that a change in Ca^{2+} concentration on either side of the membrane is mediated only through the attached SOC/CRAC polypeptide. Preferably, a SOC/CRAC polypeptide is expressed in an intact cell and is present on the cell-membrane (as in physiologic conditions). The cell expressing the SOC/CRAC polypeptide is preferably a eukaryotic cell, and the SOC/CRAC polypeptide is preferably recombinantly expressed, although cells naturally expressing a SOC/CRAC polypeptide may also be used. Synthetic membranes, however, containing SOC/CRAC polypeptides may also be used. See, e.g., K. Kiselyov, et al., Functional interaction between InsP3 receptors and store-operated Htrp3 channels, Nature 396, 478-82 (1998).

The cell expressing the SOC/CRAC polypeptide is incubated under conditions which, in the absence of the candidate agent, permit calcium flux into the cell and allow detection of a reference calcium concentration. For example, depletion of intracellular calcium stores with thapsigargin or other agents (Putney, J.W. Jr., in Capacitative Calcium Entry, R.G. Landes Co. and Chapman & Hall, 1997) would produce a given level of SOC/CRAC channel activation and a given reference calcium concentration. Detection of a decrease in the

foregoing activities (i.e., a decrease in the intracellular calcium concentration) relative to the reference calcium concentration indicates that the candidate agent is a lead compound for an agent to inhibit SOC/CRAC calcium channel activity. Preferred SOC/CRAC polypeptides include the polypeptides of claim 15.

SOC/CRAC fragments used in the methods, when not produced by a transfected nucleic acid are added to an assay mixture as an isolated polypeptide. SOC/CRAC polypeptides preferably are produced recombinantly, although such polypeptides may be isolated from biological extracts or chemically synthesized. Recombinantly produced SOC/CRAC polypeptides include chimeric proteins comprising a fusion of a SOC/CRAC protein with another polypeptide, e.g., a polypeptide capable of providing or enhancing protein-protein binding, sequence specific nucleic acid binding (such as GAL4), enhancing stability of the SOC/CRAC polypeptide under assay conditions, or providing a detectable moiety, such as green fluorescent protein or Flag epitope.

The assay mixture is comprised of a SOC/CRAC polypeptide binding target (candidate agent) capable of interacting with a SOC/CRAC polypeptide. While natural SOC/CRAC binding targets may be used, it is frequently preferred to use portions (e.g., peptides or nucleic acid fragments) or analogs (i.e., agents which mimic the SOC/CRAC binding properties of the natural binding target for purposes of the assay) of the SOC/CRAC binding target so long as the portion or analog provides binding affinity and avidity to the SOC/CRAC polypeptide (or fragment thereof) measurable in the assay.

The assay mixture also comprises a candidate agent (binding target, e.g., agonist/antagonist). Typically, a plurality of assay mixtures are run in parallel with different agent concentrations to obtain a different response to the various concentrations. Typically, one of these concentrations serves as a negative control, i.e., at zero concentration of agent or at a concentration of agent below the limits of assay detection. Candidate agents encompass numerous chemical classes, although typically they are organic compounds. Preferably, the candidate agents are small organic compounds, i.e., those having a molecular weight of more than 50 yet less than about 2500, preferably less than about 1000 and, more preferably, less than about 500. Candidate agents comprise functional chemical groups necessary for structural interactions with polypeptides and/or nucleic acids, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups and more preferably at least three of the functional chemical groups. The candidate agents can comprise cyclic carbon or heterocyclic structure and/or aromatic or

polyaromatic structures substituted with one or more of the above-identified functional groups. Candidate agents also can be biomolecules such as peptides, saccharides, fatty acids, sterols, isoprenoids, purines, pyrimidines, derivatives or structural analogs of the above, or combinations thereof and the like. Where the agent is a nucleic acid, the agent typically is a DNA or RNA molecule, although modified nucleic acids as defined herein are also contemplated.

Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides, synthetic organic combinatorial libraries, phage display libraries of random peptides, and the like. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural and synthetically produced libraries and compounds can be readily modified through conventional chemical, physical, and biochemical means. Further, known agents may be subjected to directed or random chemical modifications such as acylation, alkylation, esterification, amidification, etc. to produce structural analogs of the agents. Non-SOC/CRAC calcium channel agonists and antagonists, for example, include agents such as dihydropyridines (DHPs), phenylalkylamines, omega conotoxin (omega.-CgTx) and pyrazonoylguanidines.

A variety of other reagents also can be included in the mixture. These include reagents such as salts, buffers, neutral proteins (e.g., albumin), detergents, etc. which may be used to facilitate optimal protein-protein, protein-nucleic acid, and/or protein/membrane component binding association. Such a reagent may also reduce non-specific or background interactions of the reaction components. Other reagents that improve the efficiency of the assay such as protease, inhibitors, nuclease inhibitors, antimicrobial agents, and the like may also be used.

The mixture of the foregoing assay materials is incubated under conditions whereby, but for the presence of the candidate agent, the SOC/CRAC polypeptide specifically binds the cellular binding target, a portion thereof or analog thereof. The order of addition of components, incubation temperature, time of incubation, and other perimeters of the assay may be readily determined. Such experimentation merely involves optimization of the assay parameters, not the fundamental composition of the assay. Incubation temperatures typically

are between 4°C and 40°C. Incubation times preferably are minimized to facilitate rapid, high throughput screening, and typically are between 0.1 and 10 hours.

After incubation, the presence or absence of specific binding between the SOC/CRAC polypeptide and one or more binding targets is detected by any convenient method available to the user. For cell free binding type assays, a separation step is often used to separate bound from unbound components. The separation step may be accomplished in a variety of ways. Conveniently, at least one of the components is immobilized on a solid substrate, from which the unbound components may be easily separated. The solid substrate can be made of a wide variety of materials and in a wide variety of shapes, e.g., microtiter plate, microbead, dipstick, resin particle, etc. The substrate preferably is chosen to maximum signal to noise ratios, primarily to minimize background binding, as well as for ease of separation and cost.

Separation may be effected for example, by removing a bead or dipstick from a reservoir, emptying or diluting a reservoir such as a microtiter plate well, rinsing a bead, particle, chromotograpic column or filter with a wash solution or solvent. The separation step preferably includes multiple rinses or washes. For example, when the solid substrate is a microtiter plate, the wells may be washed several times with a washing solution, which typically includes those components of the incubation mixture that do not participate in specific bindings such as salts, buffer, detergent, non-specific protein, etc.. Where the solid substrate is a magnetic bead, the beads may be washed one or more times with a washing solution and isolated using a magnet.

Detection may be effected in any convenient way for cell-based assays such as two- or three-hybrid screens. The transcript resulting from a reporter gene transcription assay of SOC/CRAC polypeptide interacting with a target molecule typically encodes a directly or indirectly detectable product, e.g., β-galactosidase activity, luciferase activity, and the like. For cell-free binding assays, one of the components usually comprises, or is coupled to, a detectable label. A wide variety of labels can be used, such as those that provide direct detection (e.g., radioactivity, luminescence, optical or electron density, etc.) or indirect detection (e.g., epitope tag such as the FLAG epitope, enzyme tag such as horseseradish peroxidase, etc.). The label may be bound to a SOC/CRAC binding partner, or incorporated into the structure of the binding partner.

A variety of methods may be used to detect the label, depending on the nature of the label and other assay components. For example, the label may be detected while bound to the solid substrate or subsequent to separation from the solid substrate. Labels may be directly

detected through optical or electron density, radioactive emissions, nonradiative energy transfers, etc. or indirectly detected with antibody conjugates, strepavidin-biotin conjugates, etc. Methods for detecting the labels are well known in the art.

Of particular importance in any of the foregoing assays and binding studies is the use of a specific sequence motif identified in the SOC-2/CRAC-1 polypeptide sequence as a kinase catalytic domain. According to the invention, amino acids 999-1180 of the SOC-2/CRAC-1 polypeptide (SEQ ID NO:24) (or a fragment thereof), show a localized homology with the catalytic domains of eukaryotic elongation factor-2 kinase (eEF-2 kinase, GenBank Acc. no. U93850) and *Dictyostelium* myocin heavy chain kinase A (MHCK A, GenBank Acc. no. U16856), as disclosed in Ryazanov AG, et al., *Proc Natl Acad Sci U S A*, 1997, 94(10):4884-4889. Therefore, according to the invention, a method for identifying agents useful in the modulation of SOC/CRAC polypeptide kinase activity is provided. The method involves contacting a SOC/CRAC polypeptide with kinase activity, that includes, for example, amino acids 999-1180 of the SOC-2/CRAC-1 polypeptide (SEQ ID NO:24) with a candidate agent suspected of modulating SOC/CRAC kinase activity, under conditions sufficient to allow the candidate agent to interact with the SOC/CRAC polypeptide and modulate its kinase activity; detecting a kinase activity associated with the SOC/CRAC polypeptide in the presence of the candidate agent; and comparing the kinase activity in the previous step with a control kinase activity of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the candidate agent modulates (increases or decreases) SOC/CRAC kinase activity. Other controls for kinase activity can also be performed at the same time, for example, by utilizing eEF-2 kinase and/or *Dictyostelium* MHC Kinase A, in a similar manner to the SOC/CRAC member. Methods for performing such kinase activity assays are well known in the art.

The invention thus provides SOC/CRAC-specific binding agents, methods of identifying and making such agents, and their use in diagnosis, therapy and pharmaceutical development. For example, SOC/CRAC-specific agents are useful in a variety of diagnostic and therapeutic applications, especially where disease or disease prognosis is associated with altered SOC/CRAC and SOC/CRAC calcium channel fluxing characteristics. Novel SOC/CRAC-specific binding agents include SOC/CRAC-specific antibodies and other natural intracellular and extracellular binding agents identified with assays such as two hybrid screens, and non-natural intracellular and extracellular binding agents identified in screens of chemical libraries and the like.

In general, the specificity of SOC/CRAC binding to a specific molecule is determined by binding equilibrium constants. Targets which are capable of selectively binding a SOC/CRAC polypeptide preferably have binding equilibrium constants of at least about 10^7 M^{-1}, more preferably at least about 10^8 M^{-1}, and most preferably at least about 10^9 M^{-1}. The wide variety of cell based and cell free assays may be used to demonstrate SOC/CRAC-specific binding. Cell based assays include one, two and three hybrid screens, assays in which SOC/CRAC-mediated transcription is inhibited or increased, etc. Cell free assays include SOC/CRAC-protein binding assays, immunoassays, etc. Other assays useful for screening agents which bind SOC/CRAC polypeptides include fluorescence resonance energy transfer (FRET), and electrophoretic mobility shift analysis (EMSA).

Various techniques may be employed for introducing nucleic acids of the invention into cells, depending on whether the nucleic acids are introduced *in vitro* or *in vivo* in a host. Such techniques include transfection of nucleic acid-$CaPO_4$ precipitates, transfection of nucleic acids associated with DEAE, transfection with a retrovirus including the nucleic acid of interest, liposome mediated transfection, and the like. For certain uses, it is preferred to target the nucleic acid to particular cells. In such instances, a vehicle used for delivering a nucleic acid of the invention into a cell (e.g., a retrovirus, or other virus; a liposome) can have a targeting molecule attached thereto. For example, a molecule such as an antibody specific for a surface membrane protein on the target cell or a ligand for a receptor on the target cell can be bound to or incorporated within the nucleic acid delivery vehicle. For example, where liposomes are employed to deliver the nucleic acids of the invention, proteins which bind to a surface membrane protein associated with endocytosis may be incorporated into the liposome formulation for targeting and/or to facilitate uptake. Such proteins include capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half life, and the like. Polymeric delivery systems also have been used successfully to deliver nucleic acids into cells, as is known by those skilled in the art. Such systems even permit oral delivery of nucleic acids.

Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the anti-inflammatory agent, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer base systems such as poly(lactide-glycolide), copolyoxalates, polycaprolactones,

polyesteramides, polyorthoesters, polyhydroxybutyric acid, and polyanhydrides. Microcapsules of the foregoing polymers containing drugs are described in, for example, U.S. Patent 5,075,109. Delivery systems also include non-polymer systems that are: lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono- di- and tri-glycerides; hydrogel release systems; sylastic systems; peptide based systems; wax coatings; compressed tablets using conventional binders and excipients; partially fused implants; and the like. Specific examples include, but are not limited to: (a) erosional systems in which an agent of the invention is contained in a form within a matrix such as those described in U.S. Patent Nos. 4,452,775, 4,675,189, and 5,736,152, and (b) diffusional systems in which an active component permeates at a controlled rate from a polymer such as described in U.S. Patent Nos. 3,854,480, 5,133,974 and 5,407,686. In addition, pump-based hardware delivery systems can be used, some of which are adapted for implantation.

Use of a long-term sustained release implant may be particularly suitable for treatment of chronic conditions. Long-term release, are used herein, means that the implant is constructed and arranged to delivery therapeutic levels of the active ingredient for at least 30 days, and preferably 60 days. Long-term sustained release implants are well-known to those of ordinary skill in the art and include some of the release systems described above.

The invention also contemplates gene therapy. The procedure for performing *ex vivo* gene therapy is outlined in U.S. Patent 5,399,346 and in exhibits submitted in the file history of that patent, all of which are publicly available documents. In general, it involves introduction *in vitro* of a functional copy of a gene into a cell(s) of a subject which contains a defective copy of the gene, and returning the genetically engineered cell(s) to the subject. The functional copy of the gene is under operable control of regulatory elements which permit expression of the gene in the genetically engineered cell(s). Numerous transfection and transduction techniques as well as appropriate expression vectors are well known to those of ordinary skill in the art, some of which are described in PCT application WO95/00654. *In vivo* gene therapy using vectors such as adenovirus, retroviruses, herpes virus, and targeted liposomes also is contemplated according to the invention. See, e.g., U.S. Patent Nos. 5,670,488, entitled "Adenovirus Vector for Gene Therapy", issued to Gregory et al., and 5,672,344, entitled "Viral-Mediated Gene Transfer System", issued to Kelley et al.

The invention will be more fully understood by reference to the following examples. These examples, however, are merely intended to illustrate the embodiments of the invention and are not to be construed to limit the scope of the invention.

Examples

As an initial approach to identifying SOC/CRAC channels, we considered publicly available data and hypothesized that the following characteristics are likely to be exhibited by SOC/CRAC calcium channels: i) SOC/CRAC calcium channels would be integral membrane proteins related (probably distantly) to one of the known calcium channel families (e.g. voltage gated, ligand gated, Trp), and therefore should have a pore region formed by a tetramer of 6-7 transmembrane (TM) regions; ii) high calcium selectivity was likely to come at the price of complexity, and therefore these were likely to be large proteins; iii) the high calcium selectivity of this type of channel was likely to be useful and, therefore, highly conserved; and iv) these channels should be expressed in one or more types of lymphocytes, since ICRAC is best defined in those cell types. Since the full genome of the nematode *C. elegans* is nearing completion, and IP3-dependent calcium signals have recently been shown to be required for one or more aspects of *C. elegans* development, we took the set of proteins encoded by this genome (at the time this search was initiated WORMPEP14 was the available predicted protein set) and began searching for proteins which fit the criteria above. This search began by proceeding in alphabetical order through WORMPEP14 and arbitrarily excluding all proteins below approximately 1000 amino acids in size, followed by focusing on remaining proteins with clear TM spanning regions similar to those of other calcium channels. We stopped this screen on encountering a protein designated CO5C12.3, a predicted protein of 1816 amino acids (SEQ ID NO:13). C05C12.3 was noteable because its central pore region had some sequence similarity to but was clearly distinct from members of the Trp family of calcium channels, and the hydrophobicity plot of this region showed a characteristically wide spacing between the fifth and sixth TM regions for the amino acid residues which are thought to line the channel pore region and mediate the calcium selectivity of the channels. In addition, it lacked any ankyrin repeats in the region amino-terminal to its pore region, further distinguishing it from other Trp family proteins.

We then used C05C12.3 for BLAST alignment screening of the rest of the *C. elegans* genome and also mammalian databases for homologous proteins, revealing two other *C. elegans* homologues (SEQ ID NO:14 and SEQ ID NO:15), and also a recently cloned mammalian protein named melastatin-1 (MLSN-1/SOC-1, SEQ ID NOs:9 and 10, and

GenBank Acc. No. AF071787). Using these sequences, we subsequently performed an exhaustive screening of publicly accessible EST databases in search of lymphocyte homologues, but were unsuccessful in detecting any homologous transcripts in any lymphocyte lines. Since MLSN-1 (SEQ ID NOs:9 and 10) was expressed exclusively in melanocytes and retina by Northern blot hybridization and by EST database searching, there was no evidence that this type of channel was expressed in the type of cell in which ICRAC-like currents were best defined. Subsequent BLAST searches picked up mouse EST sequence AI098310 (SEQ ID NO:22) from a monocyte cell line. The I.M.A.G.E. consortium clone containing the above-identified EST was then purchased from ATCC (clone ID. 1312756, Manassas, VA) and was further characterized. Using other portions of this sequence in EST searches, we subsequently picked up similar sequences in human B-cells (SEQ ID NOs:20 and 21), and other cell types as well (SEQ ID NOs: 11, 12, 16, 17, 18, and 19). Most of these sequences were subsequently identified to be part of the 3'-UTR or of the carboxy terminal region of the proteins, which are not readily identifiable as Trp channels, providing an explanation for the art's inability to detect any type of Trp related transcripts in lymphocytes. Partial sequences from the 5' and/or 3' ends of the above identified clones were then used to screen leukocyte and kidney cDNA libraries to extend the original sequences more toward the 5' and/or 3' ends.

In view of the foregoing, it was concluded that channels of this type were expressed in many types of lymphocytes, and therefore were members of a new family of SOC/CRAC calcium channels.

Experimental Procedures

Screening of the cDNA libraries

Leukocyte and kidney cDNA libraries from Life Technologies (Gaithersburg, MD) were screened using the Gene Trapper II methodology (Life Technologies) according to manufacturer's recommendation, using the inserts of I.M.A.G.E. clone ID nos. 1312756 and 1076485 from ATCC (Manassas, VA), under stringent hybridization conditions. Using standard methodology (*Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York), individual cDNA clones were subjected to 3-4 rounds of amplification and purification under the same hybridization conditions.

After excision from the vector and subcloning of inserts into the plasmid forms, several clones were sequenced by the Beth Israel Deaconess Medical Center's Automated

Sequencing Facility. Molecular biological techniques such as restriction enzyme treatment, subcloning, DNA extraction, bacterial culture and purification of DNA fragments were performed according to methods well known in the art. Computer analyses of protein and DNA sequences was done using "Assemblylign" (Oxford Molecular, Cambell, CA). Multiple alignments of the SOC/CRAC family members were produced using the CLUSTAL facility of the MacVector program. Restriction endonucleases, expression vectors, and modifying enzymes were purchased from commercial sources (Gibco-BRL). Sequencing vectors for DNA were purchased from Stratagene (La Jolla, CA).

Once the first members of what appeared to be a novel family of calcium channel receptors were identified and characterized, additional BLAST alignments were performed with the newly characterized nucleic acid sequences. An initial match was with genomic DNA fragment NH0332L11 (Genbank Acc. No. AC005538). Using this genomic sequence, promers were designed and a number of cDNA libraries was surveyed by PCR. A prostate specific message was identified and characterized, leading to the isolation and characterization of SOC-4/CRAC-3 (SEQ ID NOs: 31 and 32).

Functional Assays

Transient Expression of SOC/CRAC

In our initial transient expression experiments, we expressed or expect to express a SOC/CRAC molecule transiently in RBL-2H3 mast cells, Jurkat T cells, and A20 B-lymphocytes using both electroporation and vaccinia virus-driven expression, and measured the calcium influx produced by depletion of intracellular calcium stores with thapsigargin. Each of the foregoing techniques is well known to those of ordinary skill in the art and can be performed using various methods (see, e.g., Current Methods in Molecular Biology, eds. Ausubal, F.M., et al. 1987, Green Publishers and Wiley Interscience, N.Y., N.Y.). Exemplary methods are described herein.

Depletion of intracellular calcium stores is accomplished by treating the cells with 1 micromolar thapsigargin; alternative agents which function to deplete intracellular stores are described in by Putney, J.W. Jr., in Capacitative Calcium Entry, R.G. Landes Co. and Chapman & Hall, 1997 and include, for example, ionomycin, cyclopiazonic acid, and DBHQ.

Calcium influx is determined by measuring cytoplasmic calcium as indicated using the fura-2 fluorescent calcium indicator (see, e.g., G. Grynkiewicz, M. Poenie, R. Y. Tsien, A new generation of Ca2+ indicators with greatly improved fluorescence properties, J. Biol

Chem 260, 3440-50 (1985), and M. Poenie, R. Tsien, Fura-2: a powerful new tool for measuring and imaging [Ca2+]i in single cells, Prog Clin Biol Res 210, 53-6 (1986)).

Patch Clamp Analysis and Determining Selectivity of SOC/CRAC

Patch clamp analysis of cells injected with SOC/CRAC cRNA is performed by using the general patch technique as described in Neher, E., "Ion channels for communication between and within cells", Science, 1992; 256:498-502. Specific techniques for applying the patch clamp analysis to RBL cells are described in Hoth, M., and Penner, R., "Depletion of intracellular calcium stores activates a calcium current in mast cells", Nature, 1992; 355:3535-355. Additional protocols for applying the patch clamp technique to other cell types are described in Putney, J.W. Jr., in Capacitative Calcium Entry, R.G. Landes Co. and Chapman & Hall, 1997

An exemplary protocol for patch clamp analysis of SOC/CRAC molecule expressed in RBL-2H3 mast cells using a recombinant vaccinia virus is as follows. The currents elicited by store depletion are determined using the whole cell configuration (Neher, E., Science, 1992; 256:498-502). Currents in SOC/CRAC expressing cells are compared to currents in control cells expressing an irrelevant protein or a classic Trp family calcium channel known as VR1 (M. J. Caterina, et al., The capsaicin receptor: a heat-activated ion channel in the pain pathway [see comments], Nature 389, 816-24 (1997)) in order to assess the contribution of SOC/CRAC expression. In addition, the magnitude of whole cell currents in the presence of extracellular calcium (10 mM), barium (10 mM), or magnesium (10 mM) are compared to determine the relative permeability of the channels to each of these ions (Hoth, M., and Penner, R., Nature, 1992; 355:3535-355) and, thereby, determine the ionic selectivity.

Pharmacologic Behavior of SOC/CRAC

For analysis of the pharmacologic behavior of a SOC/CRAC molecule, a SOC/CRAC molecule is expressed in RBL-2H3 mast cells using a recombinant vaccinia virus, and the degree of calcium influx elicited by store depletion is monitored using a bulk spectrofluorimeter or a fluorescence microscope and the calcium sensitive dye fura-2 (G. Grynkiewicz, M. Poenie, R. Y. Tsien, A new generation of $Ca2^+$ indicators with greatly improved fluorescence properties, J Biol Chem 260, 3440-50 (1985) and M. Poenie, R. Tsien, Fura-2: a powerful new tool for measuring and imaging [Ca2+]i in single cells, Prog Clin Biol Res 210, 53-6 (1986)). The level of cytoplasmic calcium in SOC/CRAC expressing cells is compared to the level achieved in control cells expressing an irrelevant protein or a classic Trp. family calcium channels known as VR1 (M. J. Caterina, et al., The

capsaicin receptor: a heat-activated ion channel in the pain pathway [see comments], Nature 389, 816-24 (1997)). These cells then are pre-incubated with the desired pharmacologic reagent, and again the response to store depletion is monitored. Comparison of the effect of depleting stores in SOC/CRAC expressing cells relative to controls in the presence or absence of the pharmacologic reagent is used to assess the ability of that reagent to modulate SOC/CRAC activity. Sphingosine is an exemplary molecule that can be used as pharmacologic reagents for pharmacologic characterization of SOC/CRAC calcium channels. See, e.g., Mathes, C., et al., Calcium release activated calcium current as a direct target for sphingosine, J Biol Chem 273(39):25020-25030 (1998). Other non-specific calcium channel inhibitors that can be used for this purpose include SKR96365 (Calbiochem) and Lanthanum..

Bulk Calcium Assays

Bulk calcium assays can be performed in a PTI Deltascan bulk spectrofluorometer using fura-2 as described in Scharenberg AM, et al., *EMBO J*, 1995, 14(14):3385-94.

Gene Targeting

The method (and reagents) described by Buerstedde JM et al, (*Cell*, 1991, Oct 4;67(1):179-88), was used to generate "knockouts" in cells. Briefly, part of the chicken SOC-2/CRAC-1 genomic sequence coding for the transmembrane region was cloned utilizing the human sequence as the probe in a chicken library screen. Chicken SOC-2/CRAC-1 clones were isolated and characterized using standard methodology. The putative exon and domain arrangement of the chicken SOC-2/CRAC-1, is depicted in Figure 1. The exons coding for TM5 (pore region) and TM6, were replaced with promoter/antibiotic cassettes (see Figure1). These targeting vectors were then used to target (and replace) the endogenous gene in DT-40 cells (chicken B lymphocyte cells).

Results

Example 1: *Transient Expression of SOC/CRAC*

In the above-identified cell lines and using both of the foregoing expression techniques, SOC/CRAC expression enhances thapsigargin-dependent influx. In addition, SOC/CRAC expression also enhances the amount of intracellular calcium stores. That this effect is likely due to SOC/CRAC acting as a plasma membrane calcium channel can be confirmed by producing an in-frame carboxy-terminal translational fusion with green fluorescent protein followed by confocal microscopy, revealing that SOC/CRAC is expressed predominantly as a plasma membrane calcium channel.

Example 2: *Patch Clamp Analysis*

The biophysical characteristics of SOC/CRAC enhanced currents when expressed in Xenopus oocytes are determined. SOC/CRAC cRNA injection is able to enhance thapsigargin-dependent whole cell currents. In addition, SOC/CRAC does not alter the reversal potential of these currents and the determination of the P_{ca}/P_{Na} ratio shows that SOC/CRAC channels are highly calcium selective.

Example 3: *Pharmacologic Behavior of SOC/CRAC*

The pharmacologic behavior of SOC/CRAC is evaluated as described above. SOC/CRAC-enhanced influx is inhibited by sphingosine in a manner that is substantially the same as that of endogenous thapsigargin-dependent calcium influx.

Example 4: *Gene targeting*

Transfection of DT-40 cells with the foregoing targeting vectors, selection for antibiotic resistance, and screening, is collectivelly refered to, herein, as a round of targeting. For the first round of targeting SOC-2/CRAC-1, 18/24 clones with homologous recombination of the targeting construct into one of the endogenous SOC-2/CRAC-1 alleles were obtained. On the second round of targeting (in order to target the second allele and therefore generate a homozygous SOC-2/CRAC-1 mutant cell), 0/48 clones were obtained. These results indicate that a "null" SOC-2/CRAC-1 mutation is detrimental to DT-40 cells, and that SOC-2/CRAC-1 is required for cell viability.

Table I. Nucleotide Sequences with homologies to SOC/CRAC nucleic acids

Sequences with SEQ ID NOs and GenBank accession numbers:
SEQ ID NO:9, AB001535, AI226731, H18835, AA419592, AA261842, AA419407, AA592910, D86107, AI098310, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, AC005538, AA654650, AA370110, AA313170, AA493512, AI670079, AI671853.

Table II. Amino Acid Sequences with homologies to SOC/CRAC polypeptides

Sequences with SEQ ID NOs and GenBank accession numbers:
SEQ ID NO:10, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, AB001535, AA592910, D86107, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, NP003298, CAB00861, NP002411, CAA92726, CAB05572.

All references, patents, and patent documents disclosed herein are incorporated by reference herein in their entirety.

What is claimed is presented below and is followed by a Sequence Listing. We claim:

Claims

1. An isolated nucleic acid molecule, comprising:

(a) nucleic acid molecules which hybridize under stringent conditions to a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, and which code for a SOC/CRAC polypeptide;

(b) deletions, additions and substitutions of (a) which code for a respective SOC/CRAC polypeptide;

(c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) in codon sequence due to the degeneracy of the genetic code, and

(d) complements of (a), (b) or (c).

2. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:1.

3. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:27.

4. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:29.

5. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:31.

6. An isolated nucleic acid molecule selected from the group consisting of

(a) a unique fragment of a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:29, and SEQ ID NO:31,

(b) complements of (a),

provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to any sequence selected from a sequence group consisting of

(1) sequences having the SEQ. ID NOS. or GenBank accession numbers of Table I,

(2) complements of (1), and

(3) fragments of (1) and (2).

7. The isolated nucleic acid molecule of claim 6, wherein the sequence of contiguous nucleotides is selected from the group consisting of:

(1) at least two contiguous nucleotides nonidentical to the sequence group,

(2) at least three contiguous nucleotides nonidentical to the sequence group,

(3) at least four contiguous nucleotides nonidentical to the sequence group,

(4) at least five contiguous nucleotides nonidentical to the sequence group,

(5) at least six contiguous nucleotides nonidentical to the sequence group,

(6) at least seven contiguous nucleotides nonidentical to the sequence group.

8. The isolated nucleic acid molecule of claim 6, wherein the unique fragment has a size selected from the group consisting of at least: 8 nucleotides, 10 nucleotides, 12 nucleotides, 14 nucleotides, 16 nucleotides, 18 nucleotides, 20, nucleotides, 22 nucleotides, 24 nucleotides, 26 nucleotides, 28 nucleotides, 30 nucleotides, 50 nucleotides, 75 nucleotides, 100 nucleotides, and 200 nucleotides.

9. The isolated nucleic acid molecule of claim 6, wherein the molecule encodes a polypeptide which is immunogenic.

10. An expression vector comprising the isolated nucleic acid molecule of claims 1, 2, 3, 4, 5, 6, 7, 8, or 9 operably linked to a promoter.

11. A host cell transformed or transfected with the expression vector of claim 10.

12. An isolated polypeptide encoded by the isolated nucleic acid molecule according to anyone of claims 1 or 6, wherein the polypeptide comprises a SOC/CRAC polypeptide or a unique fragment thereof.

13. The isolated polypeptide of claim 12, wherein the isolated polypeptide is encoded by the isolated nucleic acid molecule of claim 2, 3, 4, or 5.

14. The isolated polypeptide of claim 13, wherein the isolated polypeptide comprises a polypeptide having the sequence of amino acids selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32.

15. An isolated polypeptide encoded by the isolated nucleic acid molecule of claim 1, 2, 3, 4, or 5, wherein the polypeptide, or unique fragment thereof is immunogenic.

16. An isolated binding polypeptide which binds selectively to a polypeptide encoded by the isolated nucleic acid molecule of claim 1, 2, 3, 4, or 5.

17. The isolated binding polypeptide of claim 16, wherein the isolated binding polypeptide binds to a polypeptide having the sequence of amino acids selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32.

18. The isolated binding polypeptide of claim 17, wherein the isolated binding polypeptide is an antibody or an antibody fragment selected from the group consisting of a Fab fragment, a $F(ab)_2$ fragment or a fragment including a CDR3 region selective for the polypeptide.

19. An isolated polypeptide, comprising a unique fragment of the polypeptide of claim 12 of sufficient length to represent a sequence unique within the human genome, provided that the fragment excludes a sequence of contiguous amino acids identified in Table II.

20. A method for isolating a SOC/CRAC molecule having SOC/CRAC calcium channel activity, comprising:

a) contacting a binding molecule that is a SOC/CRAC nucleic acid or a SOC/CRAC binding polypeptide with a sample containing one or more SOC/CRAC molecules, under conditions sufficient to form a complex of the SOC/CRAC nucleic acid or the SOC/CRAC binding polypeptide and the SOC/CRAC molecule;

b) detecting the presence of the complex;

c) isolating the SOC/CRAC molecule from the complex; and

d) determining whether the isolated SOC/CRAC molecule has SOC/CRAC calcium channel activity.

21. The method of claim 20, wherein the binding molecule is a SOC/CRAC nucleic acid.

22. The method of claim 20, wherein the binding molecule is a SOC/CRAC binding polypeptide.

23. The method of claim 21, wherein the SOC/CRAC nucleic acid comprises at least 14 nucleotides from any contiguous portion of a sequence of nucleotides selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31.

24. A method for identifying agents useful in the modulation of SOC/CRAC calcium channel activity, comprising:

a) contacting a SOC/CRAC polypeptide with a candidate agent suspected of modulating SOC/CRAC calcium channel activity, under conditions sufficient to allow the SOC/CRAC polypeptide to interact selectively with the candidate agent;

b) detecting a Ca^{2+} concentration associated with SOC/CRAC calcium channel activity of the SOC/CRAC polypeptide in the presence of the candidate agent; and

c) comparing the Ca^{2+} concentration of step (b) with a control Ca^{2+} concentration of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the candidate agent modulates SOC/CRAC calcium channel activity.

25. A method for determining the level of SOC/CRAC expression in a subject, comprising:

a) measuring the expression of SOC/CRAC in a test sample obtained from the subject, and

b) comparing the measured expression of SOC/CRAC in the test sample to the expression of the SOC/CRAC polypeptide in a control to determine the level of SOC/CRAC expression in the subject.

26. The method of claim 25, wherein the expression of SOC/CRAC in (b) is SOC/CRAC mRNA expression.

27. The method of claim 25, wherein the expression of SOC/CRAC in (b) is SOC/CRAC polypeptide expression.

28. The method of claim 25, wherein the test sample is tissue.

29. The method of claim 25, wherein the test sample is a biological fluid.

30. The method of claim 26, wherein SOC/CRAC mRNA expression is measured using the Polymerase Chain Reaction (PCR).

31. The method of claim 26, wherein SOC/CRAC mRNA expression is measured using a method selected from the group consisting of northern blotting, monoclonal antisera to SOC/CRAC and polyclonal antisera to SOC/CRAC.

32. A kit, comprising a package containing:

an agent that selectively binds to the isolated nucleic acid of claim 1 or an expression product thereof, and

a control for comparing to a measured value of binding of said agent to said isolated nucleic acid of claim 1 or expression product thereof.

33. The kit of claim 32, wherein the control comprises an epitope of the expression product of the nucleic acid of claim 1.

34. A pharmaceutical composition comprising:

a pharmaceutically effective amount of an agent comprising of an isolated nucleic acid molecule of claim 1 or an expression product thereof, and

a pharmaceutically acceptable carrier.

35. The pharmaceutical composition of claim 34, wherein the agent is an expression product of the isolated nucleic acid molecule of claim 1.

36. A method for identifying agents useful in the modulation of a SOC/CRAC polypeptide kinase activity, comprising:

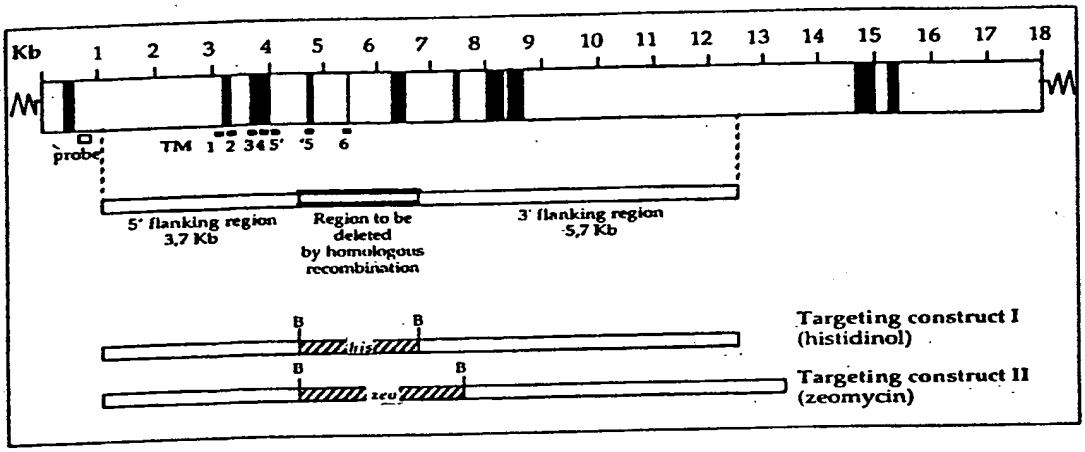
a) contacting a SOC/CRAC polypeptide with kinase activity with a candidate agent suspected of modulating SOC/CRAC kinase activity, under conditions sufficient to allow the candidate agent to interact with the SOC/CRAC polypeptide and modulate its kinase activity;

b) detecting a kinase activity associated with the SOC/CRAC polypeptide in the presence of the candidate agent; and

c) comparing the kinase activity of step (b) with a control kinase activity of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the candidate agent modulates SOC/CRAC kinase activity.

37. The method of claim 36, wherein the SOC/CRAC polypeptide comprises amino acids 999-1180 of the sequence represented as SEQ ID NO:24, or a fragment thereof that retains the kinase activity.

FIGURE 1.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probe
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5' flanking region 3,7 Kb
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SEQUENCE LISTING

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Scharenberg, Andrew

<120> CHARACTERIZATION OF A CALCIUM CHANNEL FAMILY

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<151> 1998-12-30

<150> U.S. 60/120,018
<151> 1999-01-29

<150> U.S. 60/140,415
<151> 1999-06-22

<160> 32

<170> FastSEQ for Windows Version 3.0

<210> 1
<211> 1212
<212> DNA
<213> Homo Sapiens

<400> 1
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tttggagcat ttgtaggaca cagagatagc atggatttac agaggtttaa agaaacatca 180
aacaagataa aaatactatc caataacaat acttctgaaa acactttgaa acgagtgagt 240
tctcttgctg gatttactga ctgtcacaga acttccattc ctgttcattc aaaacaagaa 300
aaaatcagta gaaggccatc taccgaagac actcatgaag tagattccaa agcagcttta 360
ataccggttt gtagatttca actaaacaga tatatattat taaatacatt aaacttttttt 420
agataagatc tacaaagtgg tgatatttgg gactatatca aaaattcaaa aaaatttttc 480
ttaagaaaac tgactttagc atagtagcag ttacagaaaa gtttcttaca gtgaatagtc 540
aggaatttta aagaaaaatt tatgcagaat aaaggcagga atctcttttt gtttgaattg 600
aagctaatta tatgaactca tttccagcta actgcgataa tgattgattt tgcaaattcc 660
ctttaaaagc acacactgac aagacaaaaa gctcaggaaa aggcagaaaa attactcctt 720
tataatcaag tattatatat aagtcagtgc tcataatttt gctcaagaaa atattgactt 780
acattcatat atatctgttc tggcatagag agattatgtt gttaaaatca tgttattgaa 840
aaaagttatt tcagtgggga aagaggttag ttaacaaaga gattcacagt aacaaatcct 900
cctttctgga gggactcttc ctgaccctga gctgcacaac tttgcaacaa attaaagcct 960
aaccgaagat gacctcacaa tggcaattta gaactcatgg gagtcaactt acataaacgg 1020
tatttgattt ctgataagat agtggaatta ttggttatag atgacaaaat aagtatgttt 1080
aaagtgatga tggacataaa aaagttttaa atataaaaca tgagaaaaga aggagatact 1140
attcaaaaag actggcaaat ttgaaaaact agaaataaaa aaaaaaaaaa aaaatgagcg 1200
gccgcaagct tt 1212

<210> 2
<211> 141
<212> PRT
<213> Homo Sapiens

<400> 2
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1 5 10 15
Ser His Leu Glu Thr Gly Thr Lys Asp Gln Glu Thr Val Cys Ser Lys
20 25 30

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        35                  40                  45
Asp Ser Met Asp Leu Gln Arg Phe Lys Glu Thr Ser Asn Lys Ile Lys
    50                  55                  60
Ile Leu Ser Asn Asn Asn Thr Ser Glu Asn Thr Leu Lys Arg Val Ser
65                  70                  75                  80
Ser Leu Ala Gly Phe Thr Asp Cys His Arg Thr Ser Ile Pro Val His
                85                  90                  95
Ser Lys Gln Glu Lys Ile Ser Arg Arg Pro Ser Thr Glu Asp Thr His
            100                 105                 110
Glu Val Asp Ser Lys Ala Ala Leu Ile Pro Val Cys Arg Phe Gln Leu
        115                 120                 125
Asn Arg Tyr Ile Leu Leu Asn Thr Leu Asn Phe Phe Arg
    130                 135                 140
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<210> 3
<211> 739
<212> DNA
<213> Homo Sapiens

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<222> (5)...(5)
<223> UNKNOWN

<221> unsure
<222> (21)...(22)
<223> UNKNOWN

<221> unsure
<222> (29)...(29)
<223> UNKNOWN

<400> 3

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gactccattt cttcaagcag tctacctctt tgwacagtat atcattatgg ttaatcttct     180
tattgcattt ytcaacaatg tgtatttaca agtgaaggca atttccaata ttgyatggaa     240
gtaccagcgt tatcatttta ttatggctta tcatgagaaa ccagttctgc ctcctccact     300
tatcattctt agccatatag tttctctgtt ttgctgcata tgtaagagaa gaaagaaaga     360
taagacttcc gatggaccaa aacttttctt aacagaagaa gatcaaaaga aacttcatga     420
ttttgaagag cagtgtgttg aaatgtattt caatgaaaaa gatgacaaat ttcattctgg     480
gagtgaagag agaattcgtg tcacttttga aagagtggaa cagatgtgca ttcagattaa     540
agaagttgga gatccgtgtc aactacataa aaagatcatt acaatcatta gattctcaaa     600
ttggccattt gcaagatctt tcagccctga cggtagatac attaaaaaca ctcactggcc     660
aaaagcgtcg gaagctagca aagttcataa tgaaatcaca cgagaactga gcatttccaa     720
acacttggct caaaaacctt                                                739
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<211> 235
<212> PRT
<213> Homo Sapiens

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<222> (41)...(41)
<223> UNKNOWN

<221> UNSURE
<222> (54)...(54)

<223> UNKNOWN

<221> UNSURE
<222> (68)...(68)
<223> UNKNOWN

<400> 4

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            20                  25                  30
Phe Leu Gln Ala Val Tyr Leu Phe Xaa Gln Tyr Ile Ile Met Val Asn
        35                  40                  45
Leu Leu Ile Ala Phe Xaa Asn Asn Val Tyr Leu Gln Val Lys Ala Ile
    50                  55                  60
Ser Asn Ile Xaa Trp Lys Tyr Gln Arg Tyr His Phe Ile Met Ala Tyr
65                  70                  75                  80
His Glu Lys Pro Val Leu Pro Pro Pro Leu Ile Ile Leu Ser His Ile
                85                  90                  95
Val Ser Leu Phe Cys Cys Ile Cys Lys Arg Arg Lys Lys Asp Lys Thr
            100                 105                 110
Ser Asp Gly Pro Lys Leu Phe Leu Thr Glu Glu Asp Gln Lys Lys Leu
        115                 120                 125
His Asp Phe Glu Glu Gln Cys Val Glu Met Tyr Phe Asn Glu Lys Asp
    130                 135                 140
Asp Lys Phe His Ser Gly Ser Glu Glu Arg Ile Arg Val Thr Phe Glu
145                 150                 155                 160
Arg Val Glu Gln Met Cys Ile Gln Ile Lys Glu Val Gly Asp Pro Cys
                165                 170                 175
Gln Leu His Lys Lys Ile Ile Thr Ile Ile Arg Phe Ser Asn Trp Pro
            180                 185                 190
Phe Ala Arg Ser Phe Ser Pro Asp Gly Arg Tyr Ile Lys Asn Thr His
        195                 200                 205
Trp Pro Lys Ala Ser Glu Ala Ser Lys Val His Asn Glu Ile Thr Arg
    210                 215                 220
Glu Leu Ser Ile Ser Lys His Leu Ala Gln Asn
225                 230                 235
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<210> 5
<211> 1579
<212> DNA
<213> Homo Sapiens

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<221> unsure
<222> (368)...(368)
<223> g or c

<221> unsure
<222> (372)...(372)
<223> g or c

<221> unsure
<222> (374)...(374)
<223> g or a

<221> unsure
<222> (375)...(375)
<223> g or c

<221> unsure
<222> (387)...(387)

<221> unsure
<222> (482)...(482)

<400> 5

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tgtaaataca cttagctcct ctcttcctca aggtgatctt gaaagtaata atccttttca     120
ttgtaatatt ttaatgaaag atgacaaaga tccccagtgt aatatatttg gtcaagactt     180
acctgcagta ccccagagaa aagaatttaa ttttccagag gctggttcct cttctggtgc     240
cttattccca agtgctgttt cccctccaga actgcgacag agactacatg gggtagaact     300
cttaaaaata tttaataaaa atcaaaaatt aggcagttca tctactagca taccacatct     360
gtcatccsca csarscaaat tttttgntag tacaccatct cagccaagtt gcaaaagcca     420
cttggaaact ggaaccaaag atcaagaaac tgtttgctct aaagctacag aaggagataa     480
tncagaattt ggagcatttg taggacacag agatagcatg gatttacaga ggtttaaaga     540
aacatcaaac aagataaaaa tactatccaa taacaatact tctgaaaaca ctttgaaacg     600
agtgagttct cttgctggat ttactgactg tcacagaact tccattcctg ttcattcaaa     660
acaagaaaaa atcagtagaa ggccatctac cgaagacact catgaagtag attccaaagc     720
agctttaata ccggtttgta gatttcaact aaacagatat atattattaa atacattaaa     780
ctttttaga taagatctac aaagtggtga tatttgggac tatatcaaaa attcaaaaaa     840
atttttctta agaaaactga ctttagcata gtagcagtta cagaaaagtt tcttacagtg     900
aatagtcagg aattttaaag aaaaatttat gcagaataaa ggcaggaatc tctttttgtt     960
tgaattgaag ctaattatat gaactcattt ccagctaact gcgataatga ttgattttgc    1020
aaattccctt taaaagcaca cactgacaag acaaaaagct caggaaaagg cagaaaaatt    1080
actcctttat aatcaagtat tatatataag tcagtgctca taattttgct caagaaaata    1140
ttgacttaca ttcatatata tctgttctgg catagagaga ttatgttgtt aaaatcatgt    1200
tattgaaaaa agttatttca gtggggaaag aggttagtta acaaagagat tcacagtaac    1260
aaatcctcct ttctggaggg actcttcctg accctgagct gcacaacttt gcaacaaatt    1320
aaagcctaac cgaagatgac ctcacaatgg caatttagaa ctcatgggag tcaacttaca    1380
taaacggtat ttgatttctg ataagatagt ggaattattg gttatagatg acaaaataag    1440
tatgtttaaa gtgatgatgg acataaaaaa gttttaaata taaaacatga gaaaagaagg    1500
agatactatt caaaaagact ggcaaatttg aaaaactaga aataaaaaaa aaaaaaaaaa    1560
atgagcggcc gcaagcttt                                                 1579
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<210> 6
<211> 243
<212> PRT
<213> Homo Sapiens

<220>
<221> UNSURE
<222> (103)...(105)
<223> UNKNOWN

<221> UNSURE
<222> (109)...(109)
<223> UNKNOWN

<221> UNSURE
<222> (141)...(141)
<223> UNKNOWN

<400> 6

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Asn Pro Phe His Cys Asn Ile Leu Met Lys Asp Asp Lys Asp Pro Gln
            20                  25                  30
Cys Asn Ile Phe Gly Gln Asp Leu Pro Ala Val Pro Gln Arg Lys Glu
        35                  40                  45
```

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Phe Asn Phe Pro Glu Ala Gly Ser Ser Ser Gly Ala Leu Phe Pro Ser
    50                  55                  60
Ala Val Ser Pro Pro Glu Leu Arg Gln Arg Leu His Gly Val Glu Leu
65                  70                  75                  80
Leu Lys Ile Phe Asn Lys Asn Gln Lys Leu Gly Ser Ser Ser Thr Ser
                85                  90                  95
Ile Pro His Leu Ser Ser Xaa Xaa Xaa Lys Phe Phe Xaa Ser Thr Pro
            100                 105                 110
Ser Gln Pro Ser Cys Lys Ser His Leu Glu Thr Gly Thr Lys Asp Gln
        115                 120                 125
Glu Thr Val Cys Ser Lys Ala Thr Glu Gly Asp Asn Xaa Glu Phe Gly
    130                 135                 140
Ala Phe Val Gly His Arg Asp Ser Met Asp Leu Gln Arg Phe Lys Glu
145                 150                 155                 160
Thr Ser Asn Lys Ile Lys Ile Leu Ser Asn Asn Asn Thr Ser Glu Asn
                165                 170                 175
Thr Leu Lys Arg Val Ser Ser Leu Ala Gly Phe Thr Asp Cys His Arg
            180                 185                 190
Thr Ser Ile Pro Val His Ser Lys Gln Glu Lys Ile Ser Arg Arg Pro
        195                 200                 205
Ser Thr Glu Asp Thr His Glu Val Asp Ser Lys Ala Ala Leu Ile Pro
    210                 215                 220
Val Cys Arg Phe Gln Leu Asn Arg Tyr Ile Leu Leu Asn Thr Leu Asn
225                 230                 235                 240
Phe Phe Arg
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<210> 7
<211> 3532
<212> DNA
<213> Mus Musculus

<220>
<221> unsure
<222> (2420)...(2420)
<223> unknown

<221> unsure
<222> (2434)...(2434)
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<221> unsure
<222> (2461)...(2461)
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<221> unsure
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<221> unsure
<222> (2470)...(2470)
<223> unknown

<400> 7

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aaacttttct taacagaaga agatcaaaag aaactccatg attttgaaga gcagtgtgtt     180
gagatgtact ttgatgagaa agatgacaaa ttcaattctg ggagtgaaga gagaatccgg     240
gtcacttttg aaagagtgga gcagatgagc attcagatta aagaagttgg agatcgtgtc     300
aactacataa aaagatcatt acagtcttta gattctcaaa ttggtcatct gcaagatctc     360
```

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tcagccctaa cagtagatac attgaaaaca cttacagccc agaaagcttc agaagctagt     420
aaagtgcaca atgagatcac acgagaattg agtatttcca aacacttggc tcagaatctt     480
attgatgatg ttcctgtaag acctttgtgg gaagaaccta gtgctgtaaa cacactgagt     540
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aaagatgaaa aagaccccca atataatctg tttggacaag atttgcccgt gataccccag     660
agaaaagaat tcaacattcc agaggctggt tcctcctgtg gtgccttatt cccaagtgct     720
gtttctcccc cagaattacg acagagacga catggggtag aaatgttaaa aatatttaat     780
aaaaatcaaa aattaggcag ttcacctaat agttcaccac atatgtcctc cccaccaacc     840
aaattttctg tgagtacccc atcccagcca agttgcaaaa gtcacttgga atccacaacc     900
aaagatcaag aacccatttt ctataaagct gcagaagggg ataacataga atttggagca     960
tttgtgggac acagagatag tatggactta cagaggttta aagaaacatc aaacaaaata    1020
agagaactgt tatctaatga tactcctgaa aacactctga aacatgtggg tgctgctgga    1080
tatagtgaat gttgtaagac ttctacttct cttcactcgg tgcaagcaga aagctgtagt    1140
agaagagcgt cgacggaaga ctctccagaa gtcgattcta aagcagcttt gttaccggat    1200
tggttacgag atagaccatc aaacagagaa atgccatctg aaggaggaac attaaatggt    1260
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aataacctga tgaggttgtc acagagtatt cccttcgttc ctgtacctcc acgaggcgag    1380
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tcagggcatc tctatatcat taagtcattt cttcctgagg tgataaacac atggtcaagc    1620
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aacttcccag atttgaagag gaatgactac acgcccttga taaaattata tttcctcagg    2160
atgagtcatc agatttgaat cttcaatctg gaaattccac caaagaatca gaagcaacaa    2220
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caactttatg ccaataaaat ctaacttaat tgcccagata tttttgcata tttagcaaca    3240
agaaaagctt atcatttgac tcaagtttta tgctttctct ttcttttcat ttcctaggta    3300
ctaattttaa tttttatttg gaaggagcag tgtaaagctt acttgtattc aatagtgtat    3360
ctcatagata cagacaaggc cgcagagata agctgttaaa tagtgtttaa tgttgatgtg    3420
gagagaaagg tgtattactt aaaaatacta taccatatac gttttgtata tcattaaatc    3480
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<210> 8
<211> 475
<212> PRT
<213> Mus Musculus

<400> 8

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            20                  25                  30
Lys Asp Lys Thr Ser Asp Gly Pro Lys Leu Phe Leu Thr Glu Glu Asp
        35                  40                  45
Gln Lys Lys Leu His Asp Phe Glu Glu Gln Cys Val Glu Met Tyr Phe
    50                  55                  60
Asp Glu Lys Asp Asp Lys Phe Asn Ser Gly Ser Glu Glu Arg Ile Arg
65                  70                  75                  80
Val Thr Phe Glu Arg Val Glu Gln Met Ser Ile Gln Ile Lys Glu Val
                85                  90                  95
Gly Asp Arg Val Asn Tyr Ile Lys Arg Ser Leu Gln Ser Leu Asp Ser
            100                 105                 110
Gln Ile Gly His Leu Gln Asp Leu Ser Ala Leu Thr Val Asp Thr Leu
        115                 120                 125
Lys Thr Leu Thr Ala Gln Lys Ala Ser Glu Ala Ser Lys Val His Asn
    130                 135                 140
Glu Ile Thr Arg Glu Leu Ser Ile Ser Lys His Leu Ala Gln Asn Leu
145                 150                 155                 160
Ile Asp Asp Val Pro Val Arg Pro Leu Trp Glu Glu Pro Ser Ala Val
                165                 170                 175
Asn Thr Leu Ser Ser Ser Leu Pro Gln Gly Asp Arg Glu Ser Asn Asn
            180                 185                 190
Pro Phe Leu Cys Asn Ile Phe Met Lys Asp Glu Lys Asp Pro Gln Tyr
        195                 200                 205
Asn Leu Phe Gly Gln Asp Leu Pro Val Ile Pro Gln Arg Lys Glu Phe
    210                 215                 220
Asn Ile Pro Glu Ala Gly Ser Ser Cys Gly Ala Leu Phe Pro Ser Ala
225                 230                 235                 240
Val Ser Pro Pro Glu Leu Arg Gln Arg Arg His Gly Val Glu Met Leu
                245                 250                 255
Lys Ile Phe Asn Lys Asn Gln Lys Leu Gly Ser Ser Pro Asn Ser Ser
            260                 265                 270
Pro His Met Ser Ser Pro Pro Thr Lys Phe Ser Val Ser Thr Pro Ser
        275                 280                 285
Gln Pro Ser Cys Lys Ser His Leu Glu Ser Thr Thr Lys Asp Gln Glu
    290                 295                 300
Pro Ile Phe Tyr Lys Ala Ala Glu Gly Asp Asn Ile Glu Phe Gly Ala
305                 310                 315                 320
Phe Val Gly His Arg Asp Ser Met Asp Leu Gln Arg Phe Lys Glu Thr
                325                 330                 335
Ser Asn Lys Ile Arg Glu Leu Leu Ser Asn Asp Thr Pro Glu Asn Thr
            340                 345                 350
Leu Lys His Val Gly Ala Ala Gly Tyr Ser Glu Cys Cys Lys Thr Ser
        355                 360                 365
Thr Ser Leu His Ser Val Gln Ala Glu Ser Cys Ser Arg Arg Ala Ser
    370                 375                 380
Thr Glu Asp Ser Pro Glu Val Asp Ser Lys Ala Ala Leu Leu Pro Asp
385                 390                 395                 400
Trp Leu Arg Asp Arg Pro Ser Asn Arg Glu Met Pro Ser Glu Gly Gly
                405                 410                 415
Thr Leu Asn Gly Leu Ala Ser Pro Phe Lys Pro Val Leu Asp Thr Asn
            420                 425                 430
Tyr Tyr Tyr Ser Ala Val Glu Arg Asn Asn Leu Met Arg Leu Ser Gln
        435                 440                 445
Ser Ile Pro Phe Val Pro Val Pro Pro Arg Gly Glu Pro Val Thr Val
    450                 455                 460
Tyr Pro Ser Gly Gly Arg Val Leu Pro Val Tyr
465                 470                 475
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<210> 9
<211> 5433
<212> DNA
<213> Mus Musculus

<220>
<221> unsure
<222> (5094)...(5094)
<223> unknown

<400> 9

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ctaacaggtg ttgctgtggc cagttcacca accagcatat ccccccctctg ccaagtgcaa     180
cacccagcaa aaatgaagag gaaagcaaac aggtggagac tcagcctgag aaatggtctg     240
ttgccaagca cacccagagc tacccaacag attcctatgg agttcttgaa ttccagggtg     300
gcggatattc caataaagcc atgtatatcc gtgtatccta tgacaccaag ccagactcac     360
tgctccatct catggtgaaa gattggcagc tggaactccc caagctctta atatctgtgc     420
atggaggcct ccagaacttt gagatgcagc ccaagctgaa acaagtcttt gggaaaggcc     480
tgatcaaggc tgctatgacc accggggcct ggatcttcac cgggggtgtc agcacaggtg     540
ttatcagcca cgtaggggat gccttgaaag accactcctc caagtccaga ggccgggttt     600
gtgctatagg aattgctcca tggggcatcg tggagaataa ggaagacctg gttggaaagg     660
 atgtaacaag agtgtaccag accatgtcca accctctaag taagctctct gtgctcaaca     720
actcccacac ccacttcatc ctggctgaca atggcaccct gggcaagtat ggcgccgagg     780
tgaagctgcg aaggctgctg gaaaagcaca tctccctcca gaagatcaac acaagactgg     840
ggcagggcgt gcccctcgtg ggtctcgtgg tggaggggg ccctaacgtg gtgtccatcg     900
tcttggaata cctgcaagaa gagcctccca tccctgtggt gatttgtgat ggcagcggac     960
gtgcctcgga catcctgtcc tttgcgcaca agtactgtga agaaggcgga ataataaatg    1020
agtccctcag ggagcagctt ctagttacca ttcagaaaac atttaattat aataaggcac    1080
 aatcacatca gctgtttgca attataatgg agtgcatgaa gaagaaagaa ctcgtcactg    1140
tgttcagaat gggttctgag ggccagcagg acatcgagat ggcaatttta actgccctgc    1200
 tgaaaggaac aaacgtatct gctccagatc agctgagctt ggcactggct tggaaccgcg    1260
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tggcaccccc gacggacagc aaagccacgg agaaggagaa gaagccaccc atggccacca    1380
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Val His Gly Gly Leu Gln Asn Phe Glu Met Gln Pro Lys Leu Lys Gln
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Lys Asp Val Thr Arg Val Tyr Gln Thr Met Ser Asn Pro Leu Ser Lys
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Val Pro Leu Val Gly Leu Val Val Glu Gly Gly Pro Asn Val Val Ser
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Cys Asp Gly Ser Gly Arg Ala Ser Asp Ile Leu Ser Phe Ala His Lys
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Gln Asn Gln Pro Tyr Met Gly Tyr Gly Arg Val Ile Tyr Cys Val Asp
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Ile Ile Phe Trp Tyr Ile Arg Val Leu Asp Ile Phe Gly Val Asn Lys
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actgcgtggg cgcgggagcc tcagctgctt cggacccaac cacacgctgt accccatggt 4500
cacgcggtgg aggcggaacg aggatggagc catctgcagg aagagcataa agaagatgct 4560
ggaagtgctg gtggtgaagc tccctctctc cgagcactgg gccctgcctg ggggctcccg 4620
ggagccaggg gagatgctac ctcggaagct gaagcggatc ctccggcagg agcactggcc 4680
gtcttttgaa aacttgctga agtgcggcat ggaggtgtac aaaggctaca tggatgaccc 4740
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gaatgacgtg gagctgaaca ggctgaactc taacctgcac gcctgcgact cgggggcctc 4860
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<210> 12
<211> 1503

<212> PRT
<213> Homo Sapiens

<400> 12

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Phe Glu Gly Leu Pro Arg Arg Val Thr Asp Leu Gly Met Val Ser Asn
            20                  25                  30
Leu Arg Arg Ser Asn Ser Ser Leu Phe Lys Ser Trp Arg Leu Gln Cys
        35                  40                  45
Pro Phe Gly Asn Asn Asp Lys Gln Glu Ser Leu Ser Ser Trp Ile Pro
    50                  55                  60
Glu Asn Ile Lys Lys Lys Glu Cys Val Tyr Phe Val Glu Ser Ser Lys
65                  70                  75                  80
Leu Ser Asp Ala Gly Lys Val Val Cys Gln Cys Gly Tyr Thr His Glu
                85                  90                  95
Gln His Leu Glu Glu Ala Thr Lys Pro His Thr Phe Gln Gly Thr Gln
            100                 105                 110
Trp Asp Pro Lys Lys His Val Gln Glu Met Pro Thr Asp Ala Phe Gly
        115                 120                 125
Asp Ile Val Phe Thr Gly Leu Ser Gln Lys Val Lys Lys Tyr Val Arg
    130                 135                 140
Val Ser Gln Asp Thr Pro Ser Ser Val Ile Tyr His Leu Met Thr Gln
145                 150                 155                 160
His Trp Gly Leu Asp Val Pro Asn Leu Leu Ile Ser Val Thr Gly Gly
                165                 170                 175
Ala Lys Asn Phe Asn Met Lys Pro Arg Leu Lys Ser Ile Phe Arg Arg
            180                 185                 190
Gly Leu Val Lys Val Ala Gln Thr Thr Gly Ala Trp Ile Ile Thr Gly
        195                 200                 205
Gly Ser His Thr Gly Val Met Lys Gln Val Gly Glu Ala Val Arg Asp
    210                 215                 220
Phe Ser Leu Ser Ser Ser Tyr Lys Glu Gly Glu Leu Ile Thr Ile Gly
225                 230                 235                 240
Val Ala Thr Trp Gly Thr Val His Arg Arg Glu Gly Leu Ile His Pro
                245                 250                 255
Thr Gly Ser Phe Pro Ala Glu Tyr Ile Leu Asp Glu Asp Gly Gln Gly
            260                 265                 270
Asn Leu Thr Cys Leu Asp Ser Asn His Ser His Phe Ile Leu Val Asp
        275                 280                 285
Asp Gly Thr His Gly Gln Tyr Gly Val Glu Ile Pro Leu Arg Thr Arg
    290                 295                 300
Leu Glu Lys Phe Ile Ser Glu Gln Thr Lys Glu Arg Gly Gly Val Ala
305                 310                 315                 320
Ile Lys Ile Pro Ile Val Cys Val Val Leu Glu Gly Gly Pro Gly Thr
                325                 330                 335
Leu His Thr Ile Asp Asn Ala Thr Thr Asn Gly Thr Pro Cys Val Val
            340                 345                 350
Val Glu Gly Ser Gly Arg Val Ala Asp Val Ile Ala Gln Val Ala Asn
        355                 360                 365
Leu Pro Val Ser Asp Ile Thr Ile Ser Leu Ile Gln Gln Lys Leu Ser
    370                 375                 380
Val Phe Phe Gln Glu Met Phe Glu Thr Phe Thr Glu Ser Arg Ile Val
385                 390                 395                 400
Glu Trp Thr Lys Lys Ile Gln Asp Ile Val Arg Arg Arg Gln Leu Leu
                405                 410                 415
Thr Val Phe Arg Glu Gly Lys Asp Gly Gln Gln Asp Val Asp Val Ala
            420                 425                 430
Ile Leu Gln Ala Leu Leu Lys Ala Ser Arg Ser Gln Asp His Phe Gly
        435                 440                 445
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His Glu Asn Trp Asp His Gln Leu Lys Leu Ala Val Ala Trp Asn Arg
    450                 455                 460
Val Asp Ile Ala Arg Ser Glu Ile Phe Met Asp Glu Trp Gln Trp Lys
465                 470                 475                 480
Pro Ser Asp Leu His Pro Thr Met Thr Ala Ala Leu Ile Ser Asn Lys
                485                 490                 495
Pro Glu Phe Val Lys Leu Phe Leu Glu Asn Gly Val Gln Leu Lys Glu
            500                 505                 510
Phe Val Thr Trp Asp Thr Leu Leu Tyr Leu Tyr Glu Asn Leu Asp Pro
        515                 520                 525
Ser Cys Leu Phe His Ser Lys Leu Gln Lys Val Leu Val Glu Asp Pro
    530                 535                 540
Glu Arg Pro Ala Cys Ala Pro Ala Ala Pro Arg Leu Gln Met His His
545                 550                 555                 560
Val Ala Gln Val Leu Arg Glu Leu Leu Gly Asp Phe Thr Gln Pro Leu
                565                 570                 575
Tyr Pro Arg Pro Arg His Asn Asp Arg Leu Arg Leu Leu Leu Pro Val
            580                 585                 590
Pro His Val Lys Leu Asn Val Gln Gly Val Ser Leu Arg Ser Leu Tyr
        595                 600                 605
Lys Arg Ser Ser Gly His Val Thr Phe Thr Met Asp Pro Ile Arg Asp
    610                 615                 620
Leu Leu Ile Trp Ala Ile Val Gln Asn Arg Arg Glu Leu Ala Gly Ile
625                 630                 635                 640
Ile Trp Ala Gln Ser Gln Asp Cys Ile Ala Ala Ala Leu Ala Cys Ser
                645                 650                 655
Lys Ile Leu Lys Glu Leu Ser Lys Glu Glu Glu Asp Thr Asp Ser Ser
            660                 665                 670
Glu Glu Met Leu Ala Leu Ala Glu Glu Tyr Glu His Arg Ala Ile Gly
        675                 680                 685
Val Phe Thr Glu Cys Tyr Arg Lys Asp Glu Glu Arg Ala Gln Lys Leu
    690                 695                 700
Leu Thr Arg Val Ser Glu Ala Trp Gly Lys Thr Thr Cys Leu Gln Leu
705                 710                 715                 720
Ala Leu Glu Ala Lys Asp Met Lys Phe Val Ser His Gly Gly Ile Gln
                725                 730                 735
Ala Phe Leu Thr Lys Val Trp Trp Gly Gln Leu Ser Val Asp Asn Gly
            740                 745                 750
Leu Trp Arg Val Thr Leu Cys Met Leu Ala Phe Pro Leu Leu Leu Thr
        755                 760                 765
Gly Leu Ile Ser Phe Arg Glu Lys Arg Leu Gln Asp Val Gly Thr Pro
    770                 775                 780
Ala Ala Arg Ala Arg Ala Phe Phe Thr Ala Pro Val Val Val Phe His
785                 790                 795                 800
Leu Asn Ile Leu Ser Tyr Phe Ala Phe Leu Cys Leu Phe Ala Tyr Val
                805                 810                 815
Leu Met Val Asp Phe Gln Pro Val Pro Ser Trp Cys Glu Cys Ala Ile
            820                 825                 830
Tyr Leu Trp Leu Phe Ser Leu Val Cys Glu Glu Met Arg Gln Leu Phe
        835                 840                 845
Tyr Asp Pro Asp Glu Cys Gly Leu Met Lys Lys Ala Ala Leu Tyr Phe
    850                 855                 860
Ser Asp Phe Trp Asn Lys Leu Asp Val Gly Ala Ile Leu Leu Phe Val
865                 870                 875                 880
Ala Gly Leu Thr Cys Arg Leu Ile Pro Ala Thr Leu Tyr Pro Gly Arg
                885                 890                 895
Val Ile Leu Ser Leu Asp Phe Ile Leu Phe Cys Leu Arg Leu Met His
            900                 905                 910
Ile Phe Thr Ile Ser Lys Thr Leu Gly Pro Lys Ile Ile Ile Val Lys
        915                 920                 925
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Arg Met Met Lys Asp Val Phe Phe Phe Leu Phe Leu Leu Ala Val Trp
930 935 940
Val Val Ser Phe Gly Val Ala Lys Gln Ala Ile Leu Ile His Asn Glu
945 950 955 960
Arg Arg Val Asp Trp Leu Phe Arg Gly Ala Val Tyr His Ser Tyr Leu
965 970 975
Thr Ile Phe Gly Gln Ile Pro Gly Tyr Ile Asp Gly Val Asn Phe Asn
980 985 990
Pro Glu His Cys Ser Pro Asn Gly Thr Asp Pro Tyr Lys Pro Lys Cys
995 1000 1005
Pro Glu Ser Asp Ala Thr Gln Gln Arg Pro Ala Phe Pro Glu Trp Leu
1010 1015 1020
Thr Val Leu Leu Leu Cys Leu Tyr Leu Leu Phe Thr Asn Ile Leu Leu
1025 1030 1035 104
Leu Asn Leu Leu Ile Ala Met Phe Asn Tyr Thr Phe Gln Gln Val Gln
1045 1050 1055
Glu His Thr Asp Gln Ile Trp Lys Phe Gln Arg His Asp Leu Ile Glu
1060 1065 1070
Glu Tyr His Gly Arg Pro Ala Ala Pro Pro Pro Phe Ile Leu Leu Ser
1075 1080 1085
His Leu Gln Leu Phe Ile Lys Arg Val Val Leu Lys Thr Pro Ala Lys
1090 1095 1100
Arg His Lys Gln Leu Lys Asn Lys Leu Glu Lys Asn Glu Glu Ala Ala
1105 1110 1115 112
Leu Leu Ser Trp Glu Ile Tyr Leu Lys Glu Asn Tyr Leu Gln Asn Arg
1125 1130 1135
Gln Phe Gln Gln Lys Gln Arg Pro Glu Gln Lys Ile Glu Asp Ile Ser
1140 1145 1150
Asn Lys Val Asp Ala Met Val Asp Leu Leu Asp Leu Asp Pro Leu Lys
1155 1160 1165
Arg Ser Gly Ser Met Glu Gln Arg Leu Ala Ser Leu Glu Glu Gln Val
1170 1175 1180
Ala Gln Thr Ala Arg Ala Leu His Trp Ile Val Arg Thr Leu Arg Ala
1185 1190 1195 120
Ser Gly Phe Ser Ser Glu Ala Asp Val Pro Thr Leu Ala Ser Gln Lys
1205 1210 1215
Ala Ala Glu Glu Pro Asp Ala Glu Pro Gly Gly Arg Lys Lys Thr Glu
1220 1225 1230
Glu Pro Gly Asp Ser Tyr His Val Asn Ala Arg His Leu Leu Tyr Pro
1235 1240 1245
Asn Cys Pro Val Thr Arg Phe Pro Val Pro Asn Glu Lys Val Pro Trp
1250 1255 1260
Glu Thr Glu Phe Leu Ile Tyr Asp Pro Pro Phe Tyr Thr Ala Glu Arg
1265 1270 1275 128
Lys Asp Ala Ala Ala Met Asp Pro Met Gly Asp Thr Leu Glu Pro Leu
1285 1290 1295
Ser Thr Ile Gln Tyr Asn Val Val Asp Gly Leu Arg Asp Arg Arg Ser
1300 1305 1310
Phe His Gly Pro Tyr Thr Val Gln Ala Gly Leu Pro Leu Asn Pro Met
1315 1320 1325
Gly Arg Thr Gly Leu Arg Gly Arg Gly Ser Leu Ser Cys Phe Gly Pro
1330 1335 1340
Asn His Thr Leu Tyr Pro Met Val Thr Arg Trp Arg Arg Asn Glu Asp
1345 1350 1355 136
Gly Ala Ile Cys Arg Lys Ser Ile Lys Lys Met Leu Glu Val Leu Val
1365 1370 1375
Val Lys Leu Pro Leu Ser Glu His Trp Ala Leu Pro Gly Gly Ser Arg
1380 1385 1390
Glu Pro Gly Glu Met Leu Pro Arg Lys Leu Lys Arg Ile Leu Arg Gln
1395 1400 1405

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Glu His Trp Pro Ser Phe Glu Asn Leu Leu Lys Cys Gly Met Glu Val
    1410                1415                1420
Tyr Lys Gly Tyr Met Asp Asp Pro Arg Asn Thr Asp Asn Ala Trp Ile
1425                1430                1435                144
Glu Thr Val Ala Val Ser Val His Phe Gln Asp Gln Asn Asp Val Glu
                1445                1450                1455
Leu Asn Arg Leu Asn Ser Asn Leu His Ala Cys Asp Ser Gly Ala Ser
            1460                1465                1470
Ile Arg Trp Gln Val Val Asp Arg Arg Ile Pro Leu Tyr Ala Asn His
        1475                1480                1485
Lys Thr Leu Leu Gln Lys Ala Ala Ala Glu Phe Gly Ala His Tyr
    1490                1495                1500
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<211> 1816
<212> PRT
<213> C. Elegans

<400> 13

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Met Ile Thr Asp Lys Asn Leu Phe Ser Arg Leu Leu Ile Lys Lys Asn
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Pro Ile Arg Met His Ser Pro Ser Phe Ser Phe Ser Leu Ile Thr Ser
            20                  25                  30
Leu Phe Phe Thr Gln Phe Phe Met Phe Gln Leu Ser Ser Met Ala Tyr
        35                  40                  45
Phe Phe Leu Thr Leu Ile Ala Gly Val Thr His Phe Tyr Phe Pro Glu
    50                  55                  60
Lys Leu Leu Gly Lys Ser Glu Asn Leu Asp His Arg Tyr Gln Ser Ser
65                  70                  75                  80
Glu Gln Lys Val Leu Ile Glu Trp Thr Glu Asn Lys Ala Val Ala Glu
                85                  90                  95
Ser Leu Arg Ala Asn Ser Val Thr Val Glu Glu Asn Glu Ser Glu Arg
            100                 105                 110
Glu Thr Glu Thr Gln Thr Lys Arg Arg Arg Lys Lys Gln Arg Ser Thr
        115                 120                 125
Ser Ser Asp Lys Ala Pro Leu Asn Ser Ala Pro Arg His Val Gln Lys
    130                 135                 140
Phe Asp Trp Lys Asp Met Leu His Leu Ala Asp Ile Ser Gly Arg Lys
145                 150                 155                 160
Arg Gly Asn Ser Thr Thr Ser His Ser Gly His Ala Thr Arg Ala Gly
                165                 170                 175
Ser Leu Lys Gly Lys Asn Trp Ile Glu Cys Arg Leu Lys Met Arg Gln
            180                 185                 190
Cys Ser Tyr Phe Val Pro Ser Gln Arg Phe Ser Glu Arg Cys Gly Cys
        195                 200                 205
Gly Lys Glu Arg Ser Lys His Thr Glu Glu Val Leu Glu Arg Ser Gln
    210                 215                 220
Asn Lys Asn His Pro Leu Asn His Leu Thr Leu Pro Gly Ile His Glu
225                 230                 235                 240
Val Asp Thr Thr Asp Ala Asp Ala Asp Asp Asn Glu Val Asn Leu Thr
                245                 250                 255
Pro Gly Arg Trp Ser Ile Gln Ser His Thr Glu Ile Val Pro Thr Asp
            260                 265                 270
Ala Tyr Gly Asn Ile Val Phe Glu Gly Thr Ala His His Ala Gln Tyr
        275                 280                 285
Ala Arg Ile Ser Phe Asp Ser Asp Pro Arg Asp Ile Val His Leu Met
    290                 295                 300
Met Lys Val Trp Lys Leu Lys Pro Pro Lys Leu Ile Ile Thr Ile Asn
305                 310                 315                 320
Gly Gly Leu Thr Lys Phe Asp Leu Gln Pro Lys Leu Ala Arg Thr Phe
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325 330 335
Arg Lys Gly Ile Met Lys Ile Ala Lys Ser Thr Asp Ala Trp Ile Ile
340 345 350
Thr Ser Gly Leu Asp Glu Gly Val Val Lys His Leu Asp Ser Ala Leu
355 360 365
His Ala Leu Glu Phe Trp Ser Phe Gly Leu Phe Trp Val Ile Gln Leu
370 375 380
Asp Val Leu Leu Ala His Ser Met Phe Ile Pro Arg Gly Ser Leu Phe
385 390 395 400
Asp His Gly Asn His Thr Ser Lys Asn His Val Val Ala Ile Gly Ile
405 410 415
Ala Ser Trp Gly Met Leu Lys Gln Arg Ser Arg Phe Val Gly Lys Asp
420 425 430
Ser Thr Val Thr Tyr Ala Thr Asn Val Phe Asn Asn Thr Arg Leu Lys
435 440 445
Glu Leu Asn Asp Asn His Ser Tyr Phe Leu Phe Ser Asp Asn Gly Thr
450 455 460
Val Asn Arg Tyr Gly Ala Glu Ile Ile Met Arg Lys Arg Leu Glu Ala
465 470 475 480
Tyr Leu Ala Gln Gly Asp Lys Lys Arg Ser Ala Ile Pro Leu Val Cys
485 490 495
Val Val Leu Glu Gly Gly Ala Phe Thr Ile Lys Met Val His Asp Tyr
500 505 510
Val Thr Thr Ile Pro Arg Ile Pro Val Ile Val Cys Asp Gly Ser Gly
515 520 525
Arg Ala Ala Asp Ile Leu Ala Phe Ala His Gln Ala Val Ser Gln Asn
530 535 540
Gly Phe Leu Ser Asp Asn Ile Arg Asn Gln Leu Val Asn Ile Val Arg
545 550 555 560
Arg Ile Phe Gly Tyr Asp Pro Lys Thr Ala Gln Lys Leu Ile Lys Gln
565 570 575
Ile Val Glu Cys Ser Thr Asn Lys Ser Leu Met Thr Ile Phe Arg Leu
580 585 590
Gly Glu Ser Ser Arg Glu Asp Leu Asp His Val Ile Met Ser Cys Leu
595 600 605
Leu Lys Gly Gln Asn Leu Ser Pro Pro Glu Gln Leu Gln Leu Ala Leu
610 615 620
Ala Trp Asn Arg Ala Asp Ile Ala Arg Thr Glu Ile Phe Ala Asn Gly
625 630 635 640
Thr Glu Trp Thr Thr Gln Asp Leu His Asn Ala Met Ile Glu Ala Leu
645 650 655
Ser Asn Asp Arg Ile Asp Phe Val His Leu Leu Leu Glu Asn Gly Val
660 665 670
Ser Met Gln Lys Phe Leu Thr Tyr Gly Arg Leu Glu His Leu Tyr Asn
675 680 685
Thr Asp Lys Gly Pro Gln Asn Thr Leu Arg Thr Asn Leu Leu Val Asp
690 695 700
Ser Lys His His Ile Lys Leu Val Glu Val Gly Arg Leu Val Glu Asn
705 710 715 720
Leu Met Gly Asn Leu Tyr Lys Ser Asn Tyr Thr Lys Glu Glu Phe Lys
725 730 735
Asn Gln Tyr Phe Leu Phe Asn Asn Arg Lys Gln Phe Gly Lys Arg Val
740 745 750
His Ser Asn Ser Asn Gly Gly Arg Asn Asp Val Ile Gly Pro Ser Gly
755 760 765
Asp Ala Gly Arg Glu Arg Met Ser Ser Met Gln Ile Ser Leu Ile Asn
770 775 780
Asn Ala Arg Asn Ser Ile Ile Ser Leu Phe Asn Gly Gly Gly Arg Lys
785 790 795 800
Arg Glu Ser Asp Asp Glu Asp Asp Phe Ser Asn Leu Glu Glu Glu Ala

805 810 815
Asn Met Asp Phe Thr Phe Arg Tyr Pro Tyr Ser Asp Leu Met Ile Trp
820 825 830
Ala Val Leu Thr Lys Arg Gln Lys Met Ala Lys Leu Met Trp Thr His
835 840 845
Gly Glu Glu Gly Met Ala Lys Ala Leu Val Ala Ser Arg Leu Tyr Val
850 855 860
Ser Leu Ala Lys Thr Ala Ser Leu Ala Thr Gly Glu Ile Gly Met Ser
865 870 875 880
Gln Asp Phe Thr Glu Phe Ser Asp Glu Phe Ser Glu Leu Ala Val Glu
885 890 895
Val Leu Glu Tyr Cys Thr Lys His Gly Arg Asp Gln Thr Leu Arg Leu
900 905 910
Leu Thr Cys Glu Leu Ala Asn Trp Gly Asp Glu Thr Cys Leu Ser Leu
915 920 925
Ala Ala Asn Asn Gly His Arg Lys Phe Leu Ala His Pro Cys Cys Gln
930 935 940
Met Leu Leu Ser Asp Leu Trp Gln Gly Gly Leu Leu Met Lys Asn Asn
945 950 955 960
Gln Asn Ser Lys Val Leu Thr Cys Leu Ala Ala Pro Pro Leu Ile Phe
965 970 975
Leu Leu Gly Phe Lys Thr Lys Glu Gln Leu Met Leu Gln Pro Lys Thr
980 985 990
Ala Ala Glu His Asp Glu Glu Met Ser Asp Ser Glu Met Asn Ser Ala
995 1000 1005
Glu Asp Thr Asp Thr Ser Ser Asp Ser Ser Ser Asp Ser Asp Asp Ser
1010 1015 1020
Asp Glu Glu Asp Ala Lys Leu Arg Ala Gln Ser Leu Ser Ala Asp Gln
1025 1030 1035 104
Pro Leu Ser Ile His Arg Leu Val Arg Asp Lys Leu Asn Phe Ser Glu
1045 1050 1055
Lys Lys Lys Pro Asp Met Gly Ile Ser Arg Ile Val Val Ala Pro Pro
1060 1065 1070
Ile Val Thr Gly Arg Asn Arg Ala Arg Thr Met Ser Ile Lys Lys Ser
1075 1080 1085
Lys Lys Asn Val Ile Lys Pro Pro Ala Cys Leu Lys Ile Glu Thr Ser
1090 1095 1100
Asp Asp Asp Glu Gln Glu Gln Lys Lys Ala Thr Glu Met Cys Lys Ser
1105 1110 1115 112
Thr Phe Phe Asp Phe Phe Phe Asp Phe Pro Tyr Ile Asn Arg Thr Gly
1125 1130 1135
Lys Arg Gly Ser Val Ala Val Ala Met Asn His Asp Asp Met Tyr Ile
1140 1145 1150
Asp Pro Ser Glu Glu Leu Asp Thr Gln Thr Arg Gln Lys Ser Ser Arg
1155 1160 1165
Glu Phe Ser Ser Ser Arg Asn Val Thr Val Gln Val Tyr Thr Gln Arg
1170 1175 1180
Pro Leu Ser Trp Lys Lys Lys Ile Met Glu Phe Tyr Lys Ala Pro Ile
1185 1190 1195 120
Thr Thr Tyr Trp Leu Trp Phe Phe Ala Phe Ile Trp Phe Leu Ile Leu
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Leu Thr Tyr Asn Leu Leu Val Lys Thr Gln Arg Ile Ala Ser Trp Ser
1220 1225 1230
Glu Trp Tyr Val Phe Ala Tyr Ile Phe Val Trp Thr Leu Glu Ile Gly
1235 1240 1245
Arg Lys Val Val Ser Thr Ile Met Met Asp Thr Ser Lys Pro Val Leu
1250 1255 1260
Lys Gln Leu Arg Val Phe Phe Phe Gln Tyr Arg Asn Gly Leu Leu Ala
1265 1270 1275 128
Phe Gly Leu Leu Thr Tyr Leu Ile Ala Tyr Phe Ile Arg Leu Ser Pro

1285 1290 1295
Thr Thr Lys Thr Leu Gly Arg Ile Leu Ile Ile Cys Asn Ser Val Ile
1300 1305 1310
Trp Ser Leu Lys Leu Val Asp Tyr Leu Ser Val Gln Gln Gly Leu Gly
1315 1320 1325
Pro Tyr Ile Asn Ile Val Ala Glu Met Ile Pro Thr Met Ile Pro Leu
1330 1335 1340
Cys Val Leu Val Phe Ile Thr Leu Tyr Ala Phe Gly Leu Leu Arg Gln
1345 1350 1355 136
Ser Ile Thr Tyr Pro Tyr Glu Asp Trp His Trp Ile Leu Val Arg Asn
1365 1370 1375
Ile Phe Leu Gln Pro Tyr Phe Met Leu Tyr Gly Glu Val Tyr Ala Ala
1380 1385 1390
Glu Ile Asp Thr Cys Gly Asp Glu Ile Trp Gln Thr His Glu Asp Glu
1395 1400 1405
Asn Ile Pro Ile Ser Met Leu Asn Val Thr His Glu Thr Cys Val Pro
1410 1415 1420
Gly Tyr Trp Ile Ala Pro Val Gly Leu Thr Val Phe Met Leu Ala Thr
1425 1430 1435 144
Asn Val Leu Leu Met Asn Val Met Val Ala Gly Cys Thr Tyr Ile Phe
1445 1450 1455
Glu Lys His Ile Gln Ser Thr Arg Glu Ile Phe Leu Phe Glu Arg Tyr
1460 1465 1470
Gly Gln Val Met Glu Tyr Glu Ser Thr Pro Trp Leu Pro Pro Pro Phe
1475 1480 1485
Thr Ile Ile Tyr His Val Ile Trp Leu Phe Lys Leu Ile Lys Ser Ser
1490 1495 1500
Ser Arg Met Phe Glu Arg Lys Asn Leu Phe Asp Gln Ser Leu Lys Leu
1505 1510 1515 152
Phe Leu Ser Pro Asp Glu Met Glu Lys Val His Thr Phe Glu Glu Glu
1525 1530 1535
Ser Val Glu Asp Met Lys Arg Glu Thr Glu Lys Lys Asn Leu Ser Ser
1540 1545 1550
Asn Asp Glu Arg Ile His Arg Thr Ala Glu Arg Thr Asp Ala Ile Leu
1555 1560 1565
Asn Arg Val Ser His Leu Thr Gln Leu Glu Phe Thr Leu Lys Glu Glu
1570 1575 1580
Ile Arg Glu Leu Glu His Lys Met Lys Asn Met Asp Ser Arg His Lys
1585 1590 1595 160
Glu Gln Met Asn Leu Met Leu Asp Met Asn Lys Lys Leu Gly Lys Phe
1605 1610 1615
Ile Ser Gly Lys Tyr Lys Arg Gly Ser Phe Gly Gly Ser Gly Ser Asp
1620 1625 1630
Gly Gly Gly Gly Ser Ser Asp Asn Ser Lys Leu Glu Pro Asn Asn Ser
1635 1640 1645
Val Pro Met Ile Thr Val Asp Gly Pro Ser Pro Ile Gly Ser Arg Arg
1650 1655 1660
Thr Ser Gly Gln Tyr Leu Lys Arg Asp Ser Leu Gln Ala Lys Lys Lys
1665 1670 1675 168
Ile Thr Glu Asn Arg Arg Ser Ser Leu Glu Gln Pro Lys Ile Pro Ser
1685 1690 1695
Ile Gln Phe Asn Leu Met Glu Asp Gln Asp Glu Ser Ala Ala Glu Ser
1700 1705 1710
Ala Thr Glu Glu Val Ser Ile Ser Ile Pro Val Pro Gln Met Arg Val
1715 1720 1725
Arg Gln Val Thr Glu Ser Asp Lys Ser Asp Leu Ser Glu Asp Asp Leu
1730 1735 1740
Ile Thr Arg Glu Asp Ala Pro Pro Thr Ser Ile Asn Leu Pro Arg Gly
1745 1750 1755 176
Pro Arg Arg His Ala Leu Tyr Ser Thr Ile Ala Asp Ala Ile Glu Thr

1765 1770 1775
Glu Asp Asp Phe Tyr Ala Asp Ser Pro Val Pro Met Pro Met Thr Pro
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Val Gln Pro Ala Asp Gly Ser Phe Phe Gly Glu Asn Asp Ser Arg Tyr
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Gln Arg Asp Asp Ser Asp Tyr Glu
1810 1815

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<212> PRT
<213> C. Elegans

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35 40 45
Ser Phe Arg Ser Asp His Leu Ser Arg Lys Ser Thr His Lys Phe Leu
50 55 60
Asp Asn Pro Asn Leu Phe Ala Ile Glu Leu Thr Glu Lys Leu Ser Pro
65 70 75 80
Pro Trp Ile Glu Asn Thr Phe Glu Lys Arg Glu Cys Ile Arg Phe Ala
85 90 95
Ala Leu Pro Lys Asp Pro Glu Arg Cys Gly Cys Gly Arg Pro Leu Ser
100 105 110
Ala His Thr Pro Ala Ser Thr Phe Phe Ser Thr Leu Pro Val His Leu
115 120 125
Leu Glu Lys Glu Gln Gln Thr Trp Thr Ile Ala Asn Asn Thr Gln Thr
130 135 140
Ser Thr Thr Asp Ala Phe Gly Thr Ile Val Phe Gln Gly Gly Ala His
145 150 155 160
Ala His Lys Ala Gln Tyr Val Arg Leu Ser Tyr Asp Ser Glu Pro Leu
165 170 175
Asp Val Met Tyr Leu Met Glu Lys Val Trp Gly Leu Glu Ala Pro Arg
180 185 190
Leu Val Ile Thr Val His Gly Gly Met Ser Asn Phe Glu Leu Glu Glu
195 200 205
Arg Leu Gly Arg Leu Phe Arg Lys Gly Met Leu Lys Ala Ala Gln Thr
210 215 220
Thr Gly Ala Trp Ile Ile Thr Ser Gly Leu Asp Ser Gly Val Val Arg
225 230 235 240
His Val Ala Lys Ala Leu Asp Glu Ala Gly Ile Ser Ala Arg Met Arg
245 250 255
Ser Gln Ile Val Thr Ile Gly Ile Ala Pro Trp Gly Val Ile Lys Arg
260 265 270
Lys Glu Arg Leu Ile Arg Gln Asn Glu His Val Tyr Tyr Asp Val His
275 280 285
Ser Leu Ser Val Asn Ala Asn Val Gly Ile Leu Asn Asp Arg His Ser
290 295 300
Tyr Phe Leu Leu Ala Asp Asn Gly Thr Val Gly Arg Phe Gly Ala Asp
305 310 315 320
Leu His Leu Arg Gln Asn Leu Glu Asn His Ile Ala Thr Phe Gly Cys
325 330 335
Asn Gly Arg Lys Val Pro Val Val Cys Thr Leu Leu Glu Gly Gly Ile
340 345 350
Ser Ser Ile Asn Ala Ile His Asp Tyr Val Thr Met Lys Pro Asp Ile
355 360 365

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Pro Ala Ile Val Cys Asp Gly Ser Gly Arg Ala Ala Asp Ile Ile Ser
    370                 375                 380
Phe Ala Ala Arg Tyr Ile Asn Ser Asp Gly Thr Phe Ala Ala Glu Val
385                 390                 395                 400
Gly Glu Lys Leu Arg Asn Leu Ile Lys Met Val Phe Pro Glu Thr Asp
                405                 410                 415
Gln Glu Glu Met Phe Arg Lys Ile Thr Glu Cys Val Ile Arg Asp Asp
            420                 425                 430
Leu Leu Arg Ile Phe Arg Tyr Gly Gln Glu Glu Glu Glu Asp Val Asp
        435                 440                 445
Phe Val Ile Leu Ser Thr Val Leu Gln Lys Gln Asn Leu Pro Pro Asp
    450                 455                 460
Glu Gln Leu Ala Leu Thr Leu Ser Trp Asn Arg Val Asp Leu Ala Lys
465                 470                 475                 480
Ser Cys Leu Phe Ser Asn Gly Arg Lys Trp Ser Ser Asp Val Leu Glu
                485                 490                 495
Lys Ala Met Asn Asp Ala Leu Tyr Trp Asp Arg Val Asp Phe Val Glu
            500                 505                 510
Cys Leu Leu Glu Asn Gly Val Ser Met Lys Asn Phe Leu Ser Ile Asn
        515                 520                 525
Arg Leu Glu Asn Leu Tyr Asn Met Asp Asp Ile Asn Ser Ala His Ser
    530                 535                 540
Val Arg Asn Trp Met Glu Asn Phe Asp Ser Met Asp Pro His Thr Tyr
545                 550                 555                 560
Leu Thr Ile Pro Met Ile Gly Gln Val Val Glu Lys Leu Met Gly Asn
                565                 570                 575
Ala Phe Gln Leu Tyr Tyr Thr Ser Arg Ser Phe Lys Gly Lys Tyr Asp
            580                 585                 590
Arg Tyr Lys Arg Ile Asn Gln Ser Ser Tyr Phe His Arg Lys Arg Lys
        595                 600                 605
Ile Val Gln Lys Glu Leu Phe Lys Lys Lys Ser Asp Asp Gln Ile Asn
    610                 615                 620
Asp Asn Glu Glu Glu Asp Phe Ser Phe Ala Tyr Pro Phe Asn Asp Leu
625                 630                 635                 640
Leu Ile Trp Ala Val Leu Thr Ser Arg His Gly Met Ala Glu Cys Met
                645                 650                 655
Trp Val His Gly Glu Asp Ala Met Ala Lys Cys Leu Leu Ala Ile Arg
            660                 665                 670
Leu Tyr Lys Ala Thr Ala Lys Ile Ala Glu Asp Glu Tyr Leu Asp Val
        675                 680                 685
Glu Glu Ala Lys Arg Leu Phe Asp Asn Ala Val Lys Cys Arg Glu Asp
    690                 695                 700
Ala Ile Glu Leu Leu Asp Gln Cys Tyr Arg Ala Asp His Asp Arg Thr
705                 710                 715                 720
Leu Arg Leu Leu Arg Met Glu Leu Pro His Trp Gly Asn Asn Asn Cys
                725                 730                 735
Leu Ser Leu Ala Val Leu Ala Asn Thr Lys Thr Phe Leu Ala His Pro
            740                 745                 750
Cys Cys Gln Ile Leu Leu Ala Glu Leu Trp His Gly Ser Leu Lys Val
        755                 760                 765
Arg Ser Gly Ser Asn Val Arg Val Leu Thr Ala Leu Ile Cys Pro Pro
    770                 775                 780
Ala Ile Leu Phe Met Ala Tyr Lys Pro Lys His Ser Lys Thr Ala Arg
785                 790                 795                 800
Leu Leu Ser Glu Glu Thr Pro Glu Gln Leu Pro Tyr Pro Arg Glu Ser
                805                 810                 815
Ile Thr Ser Thr Thr Ser Asn Arg Tyr Arg Tyr Ser Lys Gly Pro Glu
            820                 825                 830
Glu Gln Lys Glu Thr Leu Leu Glu Lys Gly Ser Tyr Thr Lys Lys Val
        835                 840                 845
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Thr Ile Ile Ser Ser Arg Lys Asn Ser Gly Val Ala Ser Val Tyr Gly
    850                 855                 860
Ser Ala Ser Ser Met Met Phe Lys Arg Glu Pro Gln Leu Asn Lys Phe
865                 870                 875                 880
Glu Arg Phe Arg Ala Phe Tyr Ser Ser Pro Ile Thr Lys Phe Trp Ser
                885                 890                 895
Trp Cys Ile Ala Phe Leu Ile Phe Leu Thr Thr Gln Thr Cys Ile Leu
            900                 905                 910
Leu Leu Glu Thr Ser Leu Lys Pro Ser Lys Tyr Glu Trp Ile Thr Phe
        915                 920                 925
Ile Tyr Thr Val Thr Leu Ser Val Glu His Ile Arg Lys Leu Met Thr
    930                 935                 940
Ser Glu Gly Ser Arg Ile Asn Glu Lys Val Lys Val Phe Tyr Ala Lys
945                 950                 955                 960
Trp Tyr Asn Ile Trp Thr Ser Ala Ala Leu Leu Phe Phe Leu Val Gly
                965                 970                 975
Tyr Gly Phe Arg Leu Val Pro Met Tyr Arg His Ser Trp Gly Arg Val
            980                 985                 990
Leu Leu Ser Phe Ser Asn Val Leu Phe Tyr Met Lys Ile Phe Glu Tyr
        995                 1000                1005
Leu Ser Val His Pro Leu Leu Gly Pro Tyr Ile Gln Met Ala Ala Lys
    1010                1015                1020
Met Val Trp Ser Met Cys Tyr Ile Cys Val Leu Leu Leu Val Pro Leu
1025                1030                1035                104
Met Ala Phe Gly Val Asn Arg Gln Ala Leu Thr Glu Pro Asn Val Lys
                1045                1050                1055
Asp Trp His Trp Leu Leu Val Arg Asn Ile Phe Tyr Lys Pro Tyr Phe
            1060                1065                1070
Met Leu Tyr Gly Glu Val Tyr Ala Gly Glu Ile Asp Thr Cys Gly Asp
        1075                1080                1085
Glu Gly Ile Arg Cys Phe Pro Gly Tyr Phe Ile Pro Pro Leu Leu Met
    1090                1095                1100
Val Ile Phe Leu Leu Val Ala Asn Ile Leu Leu Leu Asn Leu Leu Ile
1105                1110                1115                112
Ala Ile Phe Asn Asn Ile Tyr Asn Asp Ser Ile Glu Lys Ser Lys Glu
                1125                1130                1135
Ile Trp Leu Phe Gln Arg Tyr Gln Gln Leu Met Glu Tyr His Asp Ser
            1140                1145                1150
Pro Phe Leu Pro Pro Pro Phe Ser Ile Phe Ala His Val Tyr His Phe
        1155                1160                1165
Ile Asp Tyr Leu Tyr Asn Leu Arg Arg Pro Asp Thr Lys Arg Phe Arg
    1170                1175                1180
Ser Glu His Ser Ile Lys Leu Ser Val Thr Glu Asp Glu Met Lys Arg
1185                1190                1195                120
Ile Gln Asp Phe Glu Glu Asp Cys Ile Asp Thr Leu Thr Arg Ile Arg
                1205                1210                1215
Lys Leu Lys Leu Asn Thr Lys Glu Pro Leu Ser Val Thr Asp Leu Thr
            1220                1225                1230
Glu Leu Thr Cys Gln Arg Val His Asp Leu Met Gln Glu Asn Phe Leu
        1235                1240                1245
Leu Lys Ser Arg Val Tyr Asp Ile Glu Thr Lys Ile Asp His Ile Ser
    1250                1255                1260
Asn Ser Ser Asp Glu Val Val Gln Ile Leu Lys Asn Lys Lys Leu Ser
1265                1270                1275                128
Gln Asn Phe Ala Ala Ser Ser Leu Ser Leu Pro Asp Thr Ser Ile Glu
                1285                1290                1295
Val Pro Lys Ile Thr Lys Thr Leu Ile Asp Cys His Leu Ser Pro Val
            1300                1305                1310
Ser Ile Glu Asp Arg Leu Ala Thr Arg Ser Pro Leu Leu Ala Asn Leu
        1315                1320                1325
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Gln Arg Asp His Thr Leu Arg Lys Leu Pro Thr Trp Glu Thr Ser Thr
    1330                1335                1340
Ala Ser Thr Ser Ser Phe Glu Phe Val Phe Tyr Phe Thr Arg His Glu
1345                1350                1355                136
Gly Asn Glu Asn Lys Tyr Glu Phe Lys Lys Leu Glu Lys Gly Gly Phe
                1365                1370                1375
Trp Arg Asn Asn Tyr Val Ile Ser Trp Arg Leu
            1380                1385
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<210> 15
<211> 1868
<212> PRT
<213> C. Elegans

<400> 15

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Met Asn Leu Cys Tyr Arg Arg His Arg Tyr Ala Ser Ser Pro Glu Val
 1               5                  10                  15
Trp Cys Thr Met Glu Ser Asp Glu Leu Gly Val Thr Arg Tyr Leu Gln
            20                  25                  30
Ser Lys Gly Gly Asp Gln Val Pro Pro Thr Ser Thr Thr Thr Gly Gly
        35                  40                  45
Ala Gly Gly Asp Gly Asn Ala Val Pro Thr Thr Ser Gln Ala Gln Ala
    50                  55                  60
Gln Thr Phe Asn Ser Gly Arg Gln Thr Thr Gly Met Ser Ser Gly Asp
65                  70                  75                  80
Arg Leu Asn Glu Asp Val Ser Ala Thr Ala Asn Ser Ala Gln Leu Val
                85                  90                  95
Leu Pro Thr Pro Leu Phe Asn Gln Met Arg Phe Thr Glu Ser Asn Met
            100                 105                 110
Ser Leu Asn Arg His Asn Trp Val Arg Glu Thr Phe Thr Arg Arg Glu
        115                 120                 125
Cys Ser Arg Phe Ile Ala Ser Ser Arg Asp Leu His Lys Cys Gly Cys
    130                 135                 140
Gly Arg Thr Arg Asp Ala His Arg Asn Ile Pro Glu Leu Thr Ser Glu
145                 150                 155                 160
Phe Leu Arg Gln Lys Arg Ser Val Ala Ala Leu Glu Gln Gln Arg Ser
                165                 170                 175
Ile Ser Asn Val Asn Asp Asp Ile Asn Thr Gln Asn Met Tyr Thr Lys
            180                 185                 190
Arg Gly Ala Asn Glu Lys Trp Ser Leu Arg Lys His Thr Val Ser Leu
        195                 200                 205
Ala Thr Asn Ala Phe Gly Gln Val Glu Phe Gln Gly Gly Pro His Pro
    210                 215                 220
Tyr Lys Ala Gln Tyr Val Arg Val Asn Phe Asp Thr Glu Pro Ala Tyr
225                 230                 235                 240
Ile Met Ser Leu Phe Glu His Val Trp Gln Ile Ser Pro Pro Arg Leu
                245                 250                 255
Ile Ile Thr Val His Gly Gly Thr Ser Asn Phe Asp Leu Gln Pro Lys
            260                 265                 270
Leu Ala Arg Val Phe Arg Lys Gly Leu Leu Lys Ala Ala Ser Thr Thr
        275                 280                 285
Gly Ala Trp Ile Ile Thr Ser Gly Cys Asp Thr Gly Val Val Lys His
    290                 295                 300
Val Ala Ala Ala Leu Glu Gly Ala Gln Ser Ala Gln Arg Asn Lys Ile
305                 310                 315                 320
Val Cys Ile Gly Ile Ala Pro Trp Gly Leu Leu Lys Lys Arg Glu Asp
                325                 330                 335
Phe Ile Gly Gln Asp Lys Thr Val Pro Tyr Tyr Pro Ser Ser Ser Lys
            340                 345                 350
Gly Arg Phe Thr Gly Leu Asn Asn Arg His Ser Tyr Phe Leu Leu Val
```

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        355                 360                 365
Asp Asn Gly Thr Val Gly Arg Tyr Gly Ala Glu Val Ile Leu Arg Lys
    370                 375                 380
Arg Leu Glu Met Tyr Ile Ser Gln Lys Gln Lys Ile Phe Gly Gly Thr
385                 390                 395                 400
Arg Ser Val Pro Val Val Cys Val Val Leu Glu Gly Gly Ser Cys Thr
                405                 410                 415
Ile Arg Ser Val Leu Asp Tyr Val Thr Asn Val Pro Arg Val Pro Val
            420                 425                 430
Val Val Cys Asp Gly Ser Gly Arg Ala Ala Asp Leu Leu Ala Phe Ala
        435                 440                 445
His Gln Asn Val Thr Glu Asp Gly Leu Leu Pro Asp Asp Ile Arg Arg
    450                 455                 460
Gln Val Leu Leu Leu Val Glu Thr Thr Phe Gly Cys Ser Glu Ala Ala
465                 470                 475                 480
Ala His Arg Leu Leu His Glu Leu Thr Val Cys Ala Gln His Lys Asn
                485                 490                 495
Leu Leu Thr Ile Phe Arg Leu Gly Glu Gln Gly Glu His Asp Val Asp
            500                 505                 510
His Ala Ile Leu Thr Ala Leu Leu Lys Gly Gln Asn Leu Ser Ala Ala
        515                 520                 525
Asp Gln Leu Ala Leu Ala Leu Ala Trp Asn Arg Val Asp Ile Ala Arg
    530                 535                 540
Ser Asp Val Phe Ala Met Gly His Glu Trp Pro Gln Ala Ala Leu His
545                 550                 555                 560
Asn Ala Met Met Glu Ala Leu Ile His Asp Arg Val Asp Phe Val Arg
                565                 570                 575
Leu Leu Leu Glu Gln Gly Ile Asn Met Gln Lys Phe Leu Thr Ile Ser
            580                 585                 590
Arg Leu Asp Glu Leu Tyr Asn Thr Asp Lys Gly Pro Pro Asn Thr Leu
        595                 600                 605
Phe Tyr Ile Val Arg Asp Val Val Arg Val Arg Gln Gly Tyr Arg Phe
    610                 615                 620
Lys Leu Pro Asp Ile Gly Leu Val Ile Glu Lys Leu Met Gly Asn Ser
625                 630                 635                 640
Tyr Gln Cys Ser Tyr Thr Thr Ser Glu Phe Arg Asp Lys Tyr Lys Gln
                645                 650                 655
Arg Met Lys Arg Val Lys His Ala Gln Lys Lys Ala Met Gly Val Phe
            660                 665                 670
Ser Ser Arg Pro Ser Arg Thr Gly Ser Gly Ile Ala Ser Arg Gln Ser
        675                 680                 685
Thr Glu Gly Met Gly Gly Val Gly Gly Gly Ser Ser Val Ala Gly Val
    690                 695                 700
Phe Gly Asn Ser Phe Gly Asn Gln Asp Pro Pro Leu Asp Pro His Val
705                 710                 715                 720
Asn Arg Ser Ala Leu Ser Gly Ser Arg Ala Leu Ser Asn His Ile Leu
                725                 730                 735
Trp Arg Ser Ala Phe Arg Gly Asn Phe Pro Ala Asn Pro Met Arg Pro
            740                 745                 750
Pro Asn Leu Gly Asp Ser Arg Asp Cys Gly Ser Glu Phe Asp Glu Glu
        755                 760                 765
Leu Ser Leu Thr Ser Ala Ser Asp Gly Ser Gln Thr Glu Pro Asp Phe
    770                 775                 780
Arg Tyr Pro Tyr Ser Glu Leu Met Ile Trp Ala Val Leu Thr Lys Arg
785                 790                 795                 800
Gln Asp Met Ala Met Cys Met Trp Gln His Gly Glu Glu Ala Met Ala
                805                 810                 815
Lys Ala Leu Val Ala Cys Arg Leu Tyr Lys Ser Leu Ala Thr Glu Ala
            820                 825                 830
Ala Glu Asp Tyr Leu Glu Val Glu Ile Cys Glu Glu Leu Lys Lys Tyr
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        835                 840                 845
Ala Glu Glu Phe Arg Ile Leu Ser Leu Glu Leu Leu Asp His Cys Tyr
    850                 855                 860
His Val Asp Asp Ala Gln Thr Leu Gln Leu Leu Thr Tyr Glu Leu Ser
865                 870                 875                 880
Asn Trp Ser Asn Glu Thr Cys Leu Ala Leu Ala Val Ile Val Asn Asn
                885                 890                 895
Lys His Phe Leu Ala His Pro Cys Cys Gln Ile Leu Leu Ala Asp Leu
            900                 905                 910
Trp His Gly Gly Leu Arg Met Arg Thr His Ser Asn Ile Lys Val Val
        915                 920                 925
Leu Gly Leu Ile Cys Pro Pro Phe Ile Gln Met Leu Glu Phe Lys Thr
    930                 935                 940
Arg Glu Glu Leu Leu Asn Gln Pro Gln Thr Ala Ala Glu His Gln Asn
945                 950                 955                 960
Asp Met Asn Tyr Ser Ser Ser Ser Ser Ser Ser Ser Ser Ser Ser Ser
                965                 970                 975
Ser Ser Ser Ser Ser Asp Ser Ser Ser Phe Glu Asp Asp Asp Asp Glu
            980                 985                 990
Asn Asn Ala His Asn His Asp Gln Lys Arg Thr Arg Lys Thr Ser Gln
        995                 1000                1005
Gly Ser Ala Gln Ser Leu Asn Ile Thr Ser Leu Phe His Ser Arg Arg
    1010                1015                1020
Arg Lys Ala Lys Lys Asn Glu Lys Cys Asp Arg Glu Thr Asp Ala Ser
1025                1030                1035                104
Ala Cys Glu Ala Gly Asn Arg Gln Ile Gln Asn Gly Gly Leu Thr Ala
                1045                1050                1055
Glu Tyr Gly Thr Phe Gly Glu Ser Asn Gly Val Ser Pro Pro Pro Pro
            1060                1065                1070
Tyr Met Arg Ala Asn Ser Arg Ser Arg Tyr Asn Asn Arg Ser Asp Met
        1075                1080                1085
Ser Lys Thr Ser Ser Val Ile Phe Gly Ser Asp Pro Asn Leu Ser Lys
    1090                1095                1100
Leu Gln Lys Ser Asn Ile Thr Ser Thr Asp Arg Pro Asn Pro Met Glu
1105                1110                1115                112
Gln Phe Gln Gly Thr Arg Lys Ile Lys Met Arg Arg Arg Phe Tyr Glu
                1125                1130                1135
Phe Tyr Ser Ala Pro Ile Ser Thr Phe Trp Ser Trp Thr Ile Ser Phe
            1140                1145                1150
Ile Leu Phe Ile Thr Phe Phe Thr Tyr Thr Leu Leu Val Lys Thr Pro
        1155                1160                1165
Pro Arg Pro Thr Val Ile Glu Tyr Ile Leu Ile Ala Tyr Val Ala Ala
    1170                1175                1180
Phe Gly Leu Glu Gln Val Arg Lys Ile Ile Met Ser Asp Ala Lys Pro
1185                1190                1195                120
Phe Tyr Glu Lys Ile Arg Thr Tyr Val Cys Ser Phe Trp Asn Cys Val
                1205                1210                1215
Thr Ile Leu Ala Ile Ile Phe Tyr Ile Val Gly Phe Phe Met Arg Cys
            1220                1225                1230
Phe Gly Ser Val Ala Tyr Gly Arg Val Ile Leu Ala Cys Asp Ser Val
        1235                1240                1245
Leu Trp Thr Met Lys Leu Leu Asp Tyr Met Ser Val His Pro Lys Leu
    1250                1255                1260
Gly Pro Tyr Val Thr Met Ala Gly Lys Met Ile Gln Asn Met Ser Tyr
1265                1270                1275                128
Ile Ile Val Met Leu Val Val Thr Leu Leu Ser Phe Gly Leu Ala Arg
                1285                1290                1295
Gln Ser Ile Thr Tyr Pro Asp Glu Thr Trp His Trp Ile Leu Val Arg
            1300                1305                1310
Asn Ile Phe Leu Lys Pro Tyr Phe Met Leu Tyr Gly Glu Val Tyr Ala
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1315 1320 1325
Asp Glu Ile Asp Thr Cys Gly Asp Glu Ala Trp Asp Gln His Leu Glu
1330 1335 1340
Asn Gly Gly Pro Val Ile Leu Gly Asn Gly Thr Thr Gly Leu Ser Cys
1345 1350 1355 136
Val Pro Gly Tyr Trp Ile Pro Pro Leu Leu Met Thr Phe Phe Leu Leu
1365 1370 1375
Ile Ala Asn Ile Leu Leu Met Ser Met Leu Ile Ala Ile Phe Asn His
1380 1385 1390
Ile Phe Asp Ala Thr Asp Glu Met Ser Gln Gln Ile Trp Leu Phe Gln
1395 1400 1405
Arg Tyr Lys Gln Val Met Glu Tyr Glu Ser Thr Pro Phe Leu Pro Pro
1410 1415 1420
Pro Leu Thr Pro Leu Tyr His Gly Val Leu Ile Leu Gln Phe Val Arg
1425 1430 1435 144
Thr Arg Leu Ser Cys Ser Lys Ser Gln Glu Arg Asn Pro Ile Leu Leu
1445 1450 1455
Leu Lys Ile Ala Glu Leu Phe Leu Asp Asn Asp Gln Ile Glu Lys Leu
1460 1465 1470
His Asp Phe Glu Glu Asp Cys Met Glu Asp Leu Ala Arg Gln Lys Leu
1475 1480 1485
Asn Glu Lys Asn Thr Ser Asn Glu Gln Arg Ile Leu Arg Ala Asp Ile
1490 1495 1500
Arg Thr Asp Gln Ile Leu Asn Arg Leu Ile Asp Leu Gln Ala Lys Glu
1505 1510 1515 152
Ser Met Gly Arg Asp Val Ile Asn Asp Val Glu Ser Arg Leu Ala Ser
1525 1530 1535
Val Glu Lys Ala Gln Asn Glu Ile Leu Glu Cys Val Arg Ala Leu Leu
1540 1545 1550
Asn Gln Asn Asn Ala Pro Thr Ala Ile Gly Arg Cys Phe Ser Pro Ser
1555 1560 1565
Pro Asp Pro Leu Val Glu Thr Ala Asn Gly Thr Pro Gly Pro Leu Leu
1570 1575 1580
Leu Lys Leu Pro Gly Thr Asp Pro Ile Leu Glu Glu Lys Asp His Asp
1585 1590 1595 160
Ser Gly Glu Asn Ser Asn Ser Leu Pro Pro Gly Arg Ile Arg Arg Asn
1605 1610 1615
Arg Thr Ala Thr Ile Cys Gly Gly Tyr Val Ser Glu Glu Arg Asn Met
1620 1625 1630
Met Leu Leu Ser Pro Lys Pro Ser Asp Val Ser Gly Ile Pro Gln Gln
1635 1640 1645
Arg Leu Met Ser Val Thr Ser Met Asp Pro Leu Pro Leu Pro Leu Ala
1650 1655 1660
Lys Leu Ser Thr Met Ser Ile Arg Arg Arg His Glu Glu Tyr Thr Ser
1665 1670 1675 168
Ile Thr Asp Ser Ile Ala Ile Arg His Pro Glu Arg Arg Ile Arg Asn
1685 1690 1695
Asn Arg Ser Asn Ser Ser Glu His Asp Glu Ser Ala Val Asp Ser Glu
1700 1705 1710
Gly Gly Gly Asn Val Thr Ser Ser Pro Arg Lys Arg Ser Thr Arg Asp
1715 1720 1725
Leu Arg Met Thr Pro Ser Ser Gln Val Glu Glu Ser Thr Ser Arg Asp
1730 1735 1740
Gln Ile Phe Glu Ile Asp His Pro Glu His Glu Glu Asp Glu Ala Gln
1745 1750 1755 176
Ala Asp Cys Glu Leu Thr Asp Val Ile Thr Glu Glu Glu Asp Glu Glu
1765 1770 1775
Glu Asp Asp Glu Glu Asp Asp Ser His Glu Arg His His Ile His Pro
1780 1785 1790
Arg Arg Lys Ser Ser Arg Gln Asn Arg Gln Pro Ser His Thr Leu Glu

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       1795                1800                1805
Thr Asp Leu Ser Glu Gly Glu Glu Val Asp Pro Leu Asp Val Leu Lys
    1810                1815                1820
Met Lys Glu Leu Pro Ile Ile His Gln Ile Leu Asn Glu Glu Glu Gln
1825                1830                1835                184
Ala Gly Ala Pro His Ser Thr Pro Val Ile Ala Ser Pro Ser Ser Ser
                1845                1850                1855
Arg Ala Asp Leu Thr Ser Gln Lys Cys Ser Asp Val
            1860                1865
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<210> 16
<211> 489
<212> DNA
<213> Mus Musculus

<400> 16

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ccctgaaaga ctcgacttct gctgctagcg ctggagctga gttagttttg agaaggtttc      60
ccggggctgt ccttgttcgg tggcccgtgc caccgcctcc ggagacgctt tccgatagat     120
ggctgcaggc cgcggaggtg gaggaggagc cgctgccctt ccggagtccg ccccgtgagg     180
agaatgtccc agaaatcctg gatagagagc actttgacca agagggagtg tgtatatatt     240
ataccaagct ccaaagaccc tcacagatgt cttccaggat gtcagatttg tcagcaactt     300
gtcagatgtt tctgtggtcg tttggtcaag caacatgcat gctttactgc aagtcttgcc     360
atgaaatact cagatgtgaa attgggtgaa cactttaacc aggcaataga agaatggtct     420
gtggaaaagc acacggagca gagcccaaca gatgcttatg gagtcatcaa ttttcaaggg     480
ggttctcat                                                             489
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<210> 17
<211> 102
<212> PRT
<213> Mus Musculus

<400> 17

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Met Ser Gln Lys Ser Trp Ile Glu Ser Thr Leu Thr Lys Arg Glu Cys
 1               5                  10                  15
Val Tyr Ile Ile Pro Ser Ser Lys Asp Pro His Arg Cys Leu Pro Gly
            20                  25                  30
Cys Gln Ile Cys Gln Gln Leu Val Arg Cys Phe Cys Gly Arg Leu Val
        35                  40                  45
Lys Gln His Ala Cys Phe Thr Ala Ser Leu Ala Met Lys Tyr Ser Asp
    50                  55                  60
Val Lys Leu Gly Glu His Phe Asn Gln Ala Ile Glu Glu Trp Ser Val
65                  70                  75                  80
Glu Lys His Thr Glu Gln Ser Pro Thr Asp Ala Tyr Gly Val Ile Asn
                85                  90                  95
Phe Gln Gly Gly Ser His
            100
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<210> 18
<211> 410
<212> DNA
<213> Homo Sapiens

<220>
<221> unsure
<222> (6)...(6)

<221> unsure
<222> (58)...(58)

<221> unsure

<222> (89)...(89)

<221> unsure
<222> (406)...(406)

<400> 18
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cattgcctca ctgagccagc gcctgcctnc tacctcgccg acagctggaa ccagtgcgac 120
ctagtggctc tcacctgctt cctcctgggc gtgggctgcc ggctgacccc gggtttgtac 180
cacctgggcc gcactgtcct ctgcatcgac ttcatggttt tcacggtgcg gctgcttcac 240
atcttcacgg tcaacaaaca gctggggccc aagatcgtca tcgtgagcaa gatgatgaag 300
gacgtgttct tcttcctctt cttcctcggc gtgtggctgg tagctatggg ttgggccacg 360
gaggggttcc tgaggccacg ggacagtgac ttcccaagta tcctgncgcc 410

<210> 19
<211> 131
<212> PRT
<213> Homo Sapiens

<220>
<221> UNSURE
<222> (15)...(15)
<223> UNKNOWN

<221> UNSURE
<222> (25)...(25)
<223> UNKNOWN

<221> UNSURE
<222> (131)...(131)
<223> UNKNOWN

<400> 19
Ala Glu Gly Val Arg Ser Leu Ala Ser Gly Gly Pro Gly Leu Xaa His
1 5 10 15
Cys Leu Thr Glu Pro Ala Pro Ala Xaa Tyr Leu Ala Asp Ser Trp Asn
20 25 30
Gln Cys Asp Leu Val Ala Leu Thr Cys Phe Leu Leu Gly Val Gly Cys
35 40 45
Arg Leu Thr Pro Gly Leu Tyr His Leu Gly Arg Thr Val Leu Cys Ile
50 55 60
Asp Phe Met Val Phe Thr Val Arg Leu Leu His Ile Phe Thr Val Asn
65 70 75 80
Lys Gln Leu Gly Pro Lys Ile Val Ile Val Ser Lys Met Met Lys Asp
85 90 95
Val Phe Phe Phe Leu Phe Phe Leu Gly Val Trp Leu Val Ala Met Gly
100 105 110
Trp Ala Thr Glu Gly Phe Leu Arg Pro Arg Asp Ser Asp Phe Pro Ser
115 120 125
Ile Leu Xaa
130

<210> 20
<211> 389
<212> DNA
<213> Homo Sapiens

<400> 20
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caaagatcaa gaaactgttt gctctaaagc tacagaagga gataatacag aatttggagc 120

atttgtagga cacagagata gcatggattt acagaggttt aaagaaacat caaacaagat 180
aaaaatacta tccaataaca atacttctga aaacactttg aaacgagtga gttctcttgc 240
tggatttact gactgtcaca gaacttccat tcctgttcat tcaaaacgag aaaagatcag 300
tagaaggcca tctaccgaag acactcatga agtagattcc aaagcagctt taataccggt 360
ttgtagattt caactaaaca gatatatat 389

<210> 21
<211> 415
<212> DNA
<213> Homo Sapiens

<400> 21
atttctagtt tttcaaattt gccagtcttt ttgaatagta tctccttctt ttctcatgtt 60
ttatatttaa aacttttta tgtccatcat cactttaaac atacttattt tgtcatctat 120
aaccaataat tccactatct tatcagaaat caaataccgt ttatgtaagt tgactcccat 180
gagttctaaa ttgccattgt gaggtcatct tcggttaggc tttaatttgt tgcaaagttg 240
tgcagctcag ggtcaggaag agtccctcca gaaaggagga tttgttactg tgaatctctt 300
tgttaactaa cctctttccc cactgaaata actttttca ataacatgat tttaacaaca 360
taatctctct atgccagaac agatatatat gaatgtaagt caatattttc ttgag 415

<210> 22
<211> 405
<212> DNA
<213> Mus Musculus

<400> 22
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tagtttcact gttttgctgt gtatgcaaaa gaagaaagaa agataagact tccgatgggc 120
caaaactttt cttaacagaa gaagatcaaa agaaactcca tgattttgaa gagcagtgtg 180
ttgagatgta ctttgatgag aaagatgaca aattcaattc tgggagtgaa gagagaatcc 240
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        35                  40                  45
Ala Val Glu Leu Leu Glu Gln Ser Phe Arg Gln Asp Glu Thr Met Ala
    50                  55                  60
Met Lys Leu Leu Thr Tyr Glu Leu Lys Asn Trp Ser Asn Ser Thr Cys
65                  70                  75                  80
Leu Lys Leu Ala Val Ser Ser Arg Leu Arg Pro Phe Val Ala His Thr
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Ala Ile Leu Leu Leu Glu Tyr Lys Thr Lys Ala Glu Met Ser His Ile
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Pro Gln Ser Gln Asp Ala His Gln Met Thr Met Asp Asp Ser Glu Asn
145                 150                 155                 160
Asn Phe Gln Asn Ile Thr Glu Glu Ile Pro Met Glu Val Phe Lys Glu
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Val Arg Ile Leu Asp Ser Asn Glu Gly Lys Asn Glu Met Glu Ile Gln
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Met Lys Ser Lys Lys Leu Pro Ile Thr Arg Lys Phe Tyr Ala Phe Tyr
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His Ala Pro Ile Val Lys Phe Trp Phe Asn Thr Leu Ala Tyr Leu Gly
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Ile Glu Lys Val Arg Glu Ile Phe Met Ser Glu Ala Gly Lys Val Asn
            260                 265                 270
Gln Lys Ile Lys Val Trp Phe Ser Asp Tyr Phe Asn Ile Ser Asp Thr
        275                 280                 285
Ile Ala Ile Ile Ser Phe Phe Ile Gly Phe Gly Leu Arg Phe Gly Ala
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Lys Trp Asn Phe Ala Asn Ala Tyr Asp Asn His Val Phe Val Ala Gly
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Arg Leu Ile Tyr Cys Leu Asn Ile Ile Phe Trp Tyr Val Arg Leu Leu
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Asp Phe Leu Ala Val Asn Gln Gln Ala Gly Pro Tyr Val Met Met Ile
            340                 345                 350
Gly Lys Met Val Ala Asn Met Phe Tyr Ile Val Val Ile Met Ala Leu
        355                 360                 365
Val Leu Leu Ser Phe Gly Val Pro Arg Lys Ala Ile Leu Tyr Pro His
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Glu Ala Pro Ser Trp Thr Leu Ala Lys Asp Ile Val Phe His Pro Tyr
385                 390                 395                 400
Trp Met Ile Phe Gly Glu Val Tyr Ala Tyr Glu Ile Asp Val Cys Ala
                405                 410                 415
Asn Asp Ser Val Ile Pro Gln Ile Cys Gly Pro Gly Thr Trp Leu Thr
            420                 425                 430
Pro Phe Leu Gln Ala Val Tyr Leu Phe Val Gln Tyr Ile Ile Met Val
        435                 440                 445
Asn Leu Leu Ile Ala Phe Phe Asn Asn Val Tyr Leu Gln Val Lys Ala
    450                 455                 460
Ile Ser Asn Ile Val Trp Lys Tyr Gln Arg Tyr His Phe Ile Met Ala
465                 470                 475                 480
Tyr His Glu Lys Pro Val Leu Pro Pro Pro Leu Ile Ile Leu Ser His
                485                 490                 495
Ile Val Ser Leu Phe Cys Cys Ile Cys Lys Arg Arg Lys Lys Asp Lys
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Thr Ser Asp Gly Pro Lys Leu Phe Leu Thr Glu Glu Asp Gln Lys Lys
        515                 520                 525
Leu His Asp Phe Glu Glu Gln Cys Val Glu Met Tyr Phe Asn Glu Lys
    530                 535                 540
Asp Asp Lys Phe His Ser Gly Ser Glu Glu Arg Ile Arg Val Thr Phe
545                 550                 555                 560
Glu Arg Val Glu Gln Met Cys Ile Gln Ile Lys Glu Val Gly Asp Arg
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His Leu Gln Asp Leu Ser Ala Leu Thr Val Asp Thr Leu Lys Thr Leu
595 600 605
Thr Ala Gln Lys Ala Ser Glu Ala Ser Lys Val His Asn Glu Ile Thr
610 615 620
Arg Glu Leu Ser Ile Ser Lys His Leu Ala Gln Asn Leu Ile Asp Asp
625 630 635 640
Gly Pro Val Arg Pro Ser Val Trp Lys Lys His Gly Val Val Asn Thr
645 650 655
Leu Ser Ser Ser Leu Pro Gln Gly Asp Leu Glu Ser Asn Asn Pro Phe
660 665 670
His Cys Asn Ile Leu Met Lys Asp Asp Lys Asp Pro Gln Cys Asn Ile
675 680 685
Phe Gly Gln Asp Leu Pro Ala Val Pro Gln Arg Lys Glu Phe Asn Phe
690 695 700
Pro Glu Ala Gly Ser Ser Ser Gly Ala Leu Phe Pro Ser Ala Val Ser
705 710 715 720
Pro Pro Glu Leu Arg Gln Arg Leu His Gly Val Glu Leu Leu Lys Ile
725 730 735
Phe Asn Lys Asn Gln Lys Leu Gly Ser Ser Ser Thr Ser Ile Pro His
740 745 750
Leu Ser Ser Pro Pro Thr Lys Phe Phe Val Ser Thr Pro Ser Gln Pro
755 760 765
Ser Cys Lys Ser His Leu Glu Thr Gly Thr Lys Asp Gln Glu Thr Val
770 775 780
Cys Ser Lys Ala Thr Glu Gly Asp Asn Xaa Glu Phe Gly Ala Phe Val
785 790 795 800
Gly His Arg Asp Ser Met Asp Leu Gln Arg Phe Lys Glu Thr Ser Asn
805 810 815
Lys Ile Lys Ile Leu Ser Asn Asn Asn Thr Ser Glu Asn Thr Leu Lys
820 825 830
Arg Val Ser Ser Leu Ala Gly Phe Thr Asp Cys His Arg Thr Ser Ile
835 840 845
Pro Val His Ser Lys Gln Ala Glu Lys Ile Ser Arg Arg Pro Ser Thr
850 855 860
Glu Asp Thr His Glu Val Asp Ser Lys Ala Ala Leu Ile Pro Asp Trp
865 870 875 880
Leu Gln Asp Arg Pro Ser Asn Arg Glu Met Pro Ser Glu Glu Gly Thr
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Leu Asn Gly Leu Thr Ser Pro Phe Lys Pro Ala Met Asp Thr Asn Tyr
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Tyr Tyr Ser Ala Val Glu Arg Asn Asn Leu Met Arg Leu Ser Gln Ser
915 920 925
Ile Pro Phe Thr Pro Val Pro Pro Arg Gly Glu Pro Val Thr Val Tyr
930 935 940
Arg Leu Glu Glu Ser Ser Pro Asn Ile Leu Asn Asn Ser Met Ser Ser
945 950 955 960
Trp Ser Gln Leu Gly Leu Cys Ala Lys Ile Glu Phe Leu Ser Lys Glu
965 970 975
Glu Met Gly Gly Gly Leu Arg Arg Ala Val Lys Val Gln Cys Thr Trp
980 985 990
Ser Glu His Asp Ile Leu Lys Ser Gly His Leu Tyr Ile Ile Lys Ser
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Phe Leu Pro Glu Val Val Asn Thr Trp Ser Ser Ile Tyr Lys Glu Asp
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Gln Lys Leu Thr Phe Ala Phe Asn Gln Met Lys Pro Lys Ser Ile Pro
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Tyr Ser Pro Arg Phe Leu Glu Val Phe Leu Leu Tyr Cys His Ser Ala
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Gly Gln Trp Phe Ala Val Glu Glu Cys Met Thr Gly Glu Phe Arg Lys
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Tyr Asn Asn Asn Asn Gly Asp Glu Ile Ile Pro Thr Asn Thr Leu Glu
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Glu Ile Met Leu Ala Phe Ser His Trp Thr Tyr Glu Tyr Thr Arg Gly
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Glu Leu Leu Val Leu Asp Leu Gln Gly Val Gly Glu Asn Leu Thr Asp
1125 1130 1135
Pro Ser Val Ile Lys Ala Glu Glu Lys Arg Ser Cys Asp Met Val Phe
1140 1145 1150
Gly Pro Ala Asn Leu Gly Glu Asp Ala Ile Lys Asn Phe Arg Ala Lys
1155 1160 1165
His His Cys Asn Ser Cys Cys Arg Lys Leu Lys Leu Pro Asp Leu Lys
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Arg Asn Asp Tyr Thr Pro Asp Lys Ile Ile Phe Pro Gln Asp Glu Pro
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Tyr Phe Trp Glu Met Gly Ser Asn Ala Val Ser Ser Ala Leu Gly Ala
        35                  40                  45
Cys Leu Leu Leu Arg Val Met Ala Arg Leu Glu Pro Asp Ala Glu Glu
    50                  55                  60
Ala Ala Arg Arg Lys Asp Leu Ala Phe Lys Phe Glu Gly Met Gly Val
65                  70                  75                  80
Asp Leu Phe Gly Glu Cys Tyr Arg Ser Ser Glu Val Arg Ala Ala Arg
                85                  90                  95
Leu Leu Leu Arg Arg Cys Pro Leu Trp Gly Asp Ala Thr Cys Leu Gln
            100                 105                 110
Leu Ala Met Gln Ala Asp Ala Arg Ala Phe Phe Ala Gln Asp Gly Val
        115                 120                 125
Gln Ser Leu Leu Thr Gln Lys Trp Trp Gly Asp Met Ala Ser Thr Thr
    130                 135                 140
Pro Ile Trp Ala Leu Val Leu Ala Phe Phe Cys Pro Pro Leu Ile Tyr
145                 150                 155                 160
Thr Arg Leu Ile Thr Phe Arg Lys Ser Glu Glu Glu Pro Thr Arg Glu
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Glu Leu Glu Phe Asp Met Asp Ser Val Ile Asn Gly Glu Gly Pro Val
            180                 185                 190
Gly Thr Ala Asp Pro Ala Glu Lys Thr Pro Leu Gly Val Pro Arg Gln
        195                 200                 205
Ser Gly Arg Pro Gly Cys Cys Gly Gly Arg Cys Gly Gly Arg Arg Cys
    210                 215                 220
Leu Arg Arg Trp Phe His Phe Trp Gly Ala Pro Val Thr Ile Phe Met
225                 230                 235                 240
Gly Asn Val Val Ser Tyr Leu Leu Phe Leu Leu Leu Phe Ser Arg Val
                245                 250                 255
Leu Leu Val Asp Phe Gln Pro Ala Pro Pro Gly Ser Leu Glu Leu Leu
            260                 265                 270
Leu Tyr Phe Trp Ala Phe Thr Leu Leu Cys Glu Glu Leu Arg Gln Gly
        275                 280                 285
Leu Ser Gly Gly Gly Gly Ser Leu Ala Ser Gly Gly Pro Gly Pro Gly
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Cys Arg Leu Thr Pro Gly Leu Tyr His Leu Gly Arg Thr Val Leu Cys
            340                 345                 350
Ile Asp Phe Met Val Phe Thr Val Arg Leu Leu His Ile Phe Thr Val
        355                 360                 365
Asn Lys Gln Leu Gly Pro Lys Ile Val Ile Val Ser Lys Met Met Lys
    370                 375                 380
Asp Val Phe Phe Phe Leu Phe Phe Leu Gly Val Trp Leu Val Ala Tyr
385                 390                 395                 400
Gly Val Ala Thr Glu Gly Leu Leu Arg Pro Arg Asp Ser Asp Phe Pro
                405                 410                 415
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Lys Gln His Ala Cys Phe Thr Ala Ser Leu Ala Met Lys Tyr Ser Asp
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Glu Lys His Thr Glu Gln Ser Pro Thr Asp Ala Tyr Gly Val Ile Asn
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Phe Gln Gly Gly Ser His Ser Tyr Arg Ala Lys Tyr Val Arg Leu Ser
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Arg Ala Pro Asn Leu Val Val Ser Val Leu Gly Gly Ser Gly Gly Pro
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<211> 1104
<212> PRT
<213> Homo Sapiens

<400> 32

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Thr Leu Asp Ser Thr Arg Thr Leu Tyr Ser Ser Ala Ser Arg Ser Thr
            20                  25                  30
Asp Leu Ser Tyr Ser Glu Ser Asp Leu Val Asn Phe Ile Gln Ala Asn
        35                  40                  45
Phe Lys Lys Arg Glu Cys Val Phe Phe Thr Lys Asp Ser Lys Ala Thr
    50                  55                  60
Glu Asn Val Cys Lys Cys Gly Tyr Ala Gln Ser Gln His Met Glu Gly
65                  70                  75                  80
Thr Gln Ile Asn Gln Ser Glu Lys Trp Asn Tyr Lys Lys His Thr Lys
                85                  90                  95
Glu Phe Pro Thr Asp Ala Phe Gly Asp Ile Gln Phe Glu Thr Leu Gly
            100                 105                 110
Lys Lys Gly Lys Tyr Ile Arg Leu Ser Cys Asp Thr Asp Ala Glu Ile
        115                 120                 125
Leu Tyr Glu Leu Leu Thr Gln His Trp His Leu Lys Thr Pro Asn Leu
    130                 135                 140
Val Ile Ser Val Thr Gly Gly Ala Lys Asn Phe Ala Leu Lys Pro Arg
145                 150                 155                 160
Met Arg Lys Ile Phe Ser Arg Leu Ile Tyr Ile Ala Gln Ser Lys Gly
                165                 170                 175
Ala Trp Ile Leu Thr Gly Gly Thr His Tyr Gly Leu Met Lys Tyr Ile
            180                 185                 190
Gly Glu Val Val Arg Asp Asn Thr Ile Ser Arg Ser Ser Glu Glu Asn
        195                 200                 205
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Ile Val Ala Ile Gly Ile Ala Ala Trp Gly Met Val Ser Asn Arg Asp
    210                 215                 220
Thr Leu Ile Arg Asn Cys Asp Ala Glu Gly Tyr Phe Leu Ala Gln Tyr
225                 230                 235                 240
Leu Met Asp Asp Phe Thr Arg Asp Pro Leu Cys Ile Leu Asp Asn Asn
                245                 250                 255
His Thr His Leu Leu Leu Val Asp Asn Gly Cys His Gly His Pro Thr
            260                 265                 270
Val Glu Ala Lys Leu Arg Asn Gln Leu Glu Lys Tyr Ile Ser Glu Arg
        275                 280                 285
Thr Ile Gln Asp Ser Asn Tyr Gly Gly Lys Ile Pro Ile Val Cys Phe
    290                 295                 300
Ala Gln Gly Gly Gly Lys Glu Thr Leu Lys Ala Ile Asn Thr Ser Ile
305                 310                 315                 320
Lys Asn Lys Ile Pro Cys Val Val Val Glu Gly Ser Gly Gln Ile Ala
                325                 330                 335
Asp Val Ile Ala Ser Leu Val Glu Val Glu Asp Ala Leu Thr Ser Ser
            340                 345                 350
Ala Val Lys Glu Lys Leu Val Arg Phe Leu Pro Arg Thr Val Ser Arg
        355                 360                 365
Leu Pro Glu Glu Glu Thr Glu Ser Trp Ile Lys Trp Leu Lys Glu Ile
    370                 375                 380
Leu Glu Cys Ser His Leu Leu Thr Val Ile Lys Met Glu Glu Ala Gly
385                 390                 395                 400
Asp Glu Ile Val Ser Asn Ala Ile Ser Tyr Ala Leu Tyr Lys Ala Phe
                405                 410                 415
Ser Thr Ser Glu Gln Asp Lys Asp Asn Trp Asn Gly Gln Leu Lys Leu
            420                 425                 430
Leu Leu Glu Trp Asn Gln Leu Asp Leu Ala Asn Asp Glu Ile Phe Thr
        435                 440                 445
Asn Asp Arg Arg Trp Glu Ser Ala Asp Leu Gln Glu Val Met Phe Thr
    450                 455                 460
Ala Leu Ile Lys Asp Arg Pro Lys Phe Val Arg Leu Phe Leu Glu Asn
465                 470                 475                 480
Gly Leu Asn Leu Arg Lys Phe Leu Thr His Asp Val Leu Thr Glu Leu
                485                 490                 495
Phe Ser Asn His Phe Ser Thr Leu Val Tyr Arg Asn Leu Gln Ile Ala
            500                 505                 510
Lys Asn Ser Tyr Asn Asp Ala Leu Leu Thr Phe Val Trp Lys Leu Val
        515                 520                 525
Ala Asn Phe Arg Arg Gly Phe Arg Lys Glu Asp Arg Asn Gly Arg Asp
    530                 535                 540
Glu Met Asp Ile Glu Leu His Asp Val Ser Pro Ile Thr Arg His Pro
545                 550                 555                 560
Leu Gln Ala Leu Phe Ile Trp Ala Ile Leu Gln Asn Lys Lys Glu Leu
                565                 570                 575
Ser Lys Val Ile Trp Glu Gln Thr Arg Gly Cys Thr Leu Ala Ala Leu
            580                 585                 590
Gly Ala Ser Lys Leu Leu Lys Thr Leu Ala Lys Val Lys Asn Asp Ile
        595                 600                 605
Asn Ala Ala Gly Glu Ser Glu Glu Leu Ala Asn Glu Tyr Glu Thr Arg
    610                 615                 620
Ala Val Glu Leu Phe Thr Glu Cys Tyr Ser Ser Asp Glu Asp Leu Ala
625                 630                 635                 640
Glu Gln Leu Leu Val Tyr Ser Cys Glu Ala Trp Gly Gly Ser Asn Cys
                645                 650                 655
Leu Glu Leu Ala Val Glu Ala Thr Asp Gln His Phe Ile Ala Gln Pro
            660                 665                 670
Gly Val Gln Asn Phe Leu Ser Lys Gln Trp Tyr Gly Glu Ile Ser Arg
        675                 680                 685
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Asp Thr Lys Asn Trp Lys Ile Ile Leu Cys Leu Phe Ile Ile Pro Leu
    690                 695                 700
Val Gly Cys Gly Phe Val Ser Phe Arg Lys Lys Pro Val Asp Lys His
705                 710                 715                 720
Lys Lys Leu Leu Trp Tyr Tyr Val Ala Phe Phe Thr Ser Pro Phe Val
                725                 730                 735
Val Phe Ser Trp Asn Val Val Phe Tyr Ile Ala Phe Leu Leu Leu Phe
            740                 745                 750
Ala Tyr Val Leu Leu Met Asp Phe His Ser Val Pro His Pro Pro Glu
        755                 760                 765
Leu Val Leu Tyr Ser Leu Val Phe Val Leu Phe Cys Asp Glu Val Arg
    770                 775                 780
Gln Trp Tyr Val Asn Gly Val Asn Tyr Phe Thr Asp Leu Trp Asn Val
785                 790                 795                 800
Met Asp Thr Leu Gly Leu Phe Tyr Phe Ile Ala Gly Ile Val Phe Arg
                805                 810                 815
Leu His Ser Ser Asn Lys Ser Ser Leu Tyr Ser Gly Arg Val Ile Phe
            820                 825                 830
Cys Leu Asp Tyr Ile Ile Phe Thr Leu Arg Leu Ile His Ile Phe Thr
        835                 840                 845
Val Ser Arg Asn Leu Gly Pro Lys Ile Ile Met Leu Gln Arg Met Leu
    850                 855                 860
Ile Asp Val Phe Phe Phe Leu Phe Leu Phe Ala Val Trp Met Val Ala
865                 870                 875                 880
Phe Gly Val Ala Arg Gln Gly Ile Leu Arg Gln Asn Glu Gln Arg Trp
                885                 890                 895
Arg Trp Ile Phe Arg Ser Val Ile Tyr Glu Pro Tyr Leu Ala Met Phe
            900                 905                 910
Gly Gln Val Pro Ser Asp Val Asp Gly Thr Thr Tyr Asp Phe Ala His
        915                 920                 925
Cys Thr Phe Thr Gly Asn Glu Ser Lys Pro Leu Cys Val Glu Leu Asp
    930                 935                 940
Glu His Asn Leu Pro Arg Phe Pro Glu Trp Ile Thr Ile Pro Leu Val
945                 950                 955                 960
Cys Ile Tyr Met Leu Ser Thr Asn Ile Leu Leu Val Asn Leu Leu Val
                965                 970                 975
Ala Met Phe Gly Tyr Thr Val Gly Thr Val Gln Glu Asn Asn Asp Gln
            980                 985                 990
Val Trp Lys Phe Gln Arg Tyr Phe Leu Val Gln Glu Tyr Cys Ser Arg
        995                 1000                1005
Leu Asn Ile Pro Phe Pro Phe Ile Val Phe Ala Tyr Phe Tyr Met Val
    1010                1015                1020
Val Lys Lys Cys Phe Lys Cys Cys Cys Lys Glu Lys Asn Met Glu Ser
1025                1030                1035                104
Ser Val Cys Cys Phe Lys Asn Glu Asp Asn Glu Thr Leu Ala Trp Glu
                1045                1050                1055
Gly Val Met Lys Glu Asn Tyr Leu Val Lys Ile Asn Thr Lys Ala Asn
            1060                1065                1070
Asp Thr Ser Glu Glu Met Arg His Arg Phe Arg Gln Leu Asp Thr Lys
        1075                1080                1085
Leu Asn Asp Leu Lys Gly Leu Leu Lys Glu Ile Ala Asn Lys Ile Lys
    1090                1095                1100
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